

CLINICAL PRACTICE GUIDELINES: SPINAL CORD MEDICINE

Bone Health and Osteoporosis Management in Individuals with Spinal Cord Injury

Clinical Practice Guideline for Health Care Providers

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Administrative and financial support provided by Paralyzed Veterans of America
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These guidelines have been prepared based on scientific and professional information available in 2019. Users should periodically review this material to ensure that the advice herein is consistent with current reasonable clinical practice. The websites noted in this document were current at the time of publication; however, because web addresses and the information contained therein change frequently, the reader is encouraged to stay apprised of the most current information.

Consortium for Spinal Cord Medicine

Member Organizations and Steering Committee Representatives

Thomas Bryce, MD Chair

Academy of Spinal Cord Injury Professionals Nurses Section

Lisa A. Beck, MS, APRN, CNS, CRRN

Academy of Spinal Cord Injury Professionals Psychologists Social Workers and Counselors Section

Charles H. Bombardier, PhD

Academy of Spinal Cord Injury Professionals Physicians Section

Mary Ann Richmond, MD, DVM, MS

American Academy of Neurology

Peter Gorman, MD, FAAN

American Academy of Orthopedic Surgeons

E. Byron Marsolais, MD, PhD

American Academy of Physical Medicine and Rehabilitation

David Chen, MD

American Association of Neurological Surgeons

Gregory Hawryluk, MD, PhD, FRCSC

American College of Emergency Physicians

American Congress of Rehabilitation Medicine

Casey Azuero, PhD

American Occupational Therapy Association

Theresa Gregorio-Torres, OTR, MA, ATP

American Physical Therapy Association

Heidi Kosakowski, PT, DPT, PhD

American Psychological Association Division 22

Charles H. Bombardier, PhD

American Spinal Injury Association

Gregory Nemunaitis, MD

Association of Academic Physiatrists

William O. McKinley, MD

Association of Rehabilitation Nurses

Donna Williams, MSN, RN, CRRN

Christopher and Dana Reeve Foundation

Bernadette Mauro

Congress of Neurological Surgeons

Insurance Rehabilitation Study Group

Debra Mayo, RN, BS, CCM

International Spinal Cord Society

Gianna Rodriquez, MD

Paralyzed Veterans of America

Stephen Yerkovich, MD

PRAXIS

Colleen O'Connell, MD, FRCSC

Society of Critical Care Medicine

Pauline K. Park, MD, FCCM

United Spinal Association

Jane Wierbicky, RN

U.S. Department of Veterans Affairs

Stephen Burns, MD

Table of Contents

Preface.....	ii
Foreword.....	iii
Acknowledgments.....	iv
The Consortium for Spinal Cord Medicine.....	v
Panel Members.....	vi
Expert Reviewers.....	viii
Abbreviations.....	x
Glossary of Terms.....	xi
Clinicians Guide to the Clinical Practice Guideline.....	1
Executive Summary of the Recommendations.....	2
1.0 Medical History, Assessment of Fracture and Fall Risk.....	2
2.0 Laboratory Screening.....	2
3.0 Bone Density Testing with Dual-Energy X-ray Absorptiometry.....	3
4.0 Volumetric Bone Density and Bone Architecture: Peripheral Quantitative Computed Tomography and Quantitative Computed Tomography.....	3
5.0 Calcium and Vitamin D3: Diet or Supplements.....	4
6.0 Rehabilitation Therapy.....	5
7.0 Drug Therapy.....	6
8.0 Fracture Management.....	7
Methods.....	9
Population, Interventions, Comparators, Outcomes, Timing, Setting, Study Design (PICOTS).....	12
Literature Review.....	13
Data Synthesis.....	14
Recommendations and Rationales.....	22
1.0 Medical History, Assessment of Fracture and Fall Risk.....	22
2.0 Laboratory Screening.....	27
3.0 Bone Density Testing with Dual-Energy X-Ray Absorptiometry.....	33
4.0 Volumetric Bone Density and Bone Architecture: Peripheral Quantitative Computed Tomography and Quantitative Computed Tomography.....	37
5.0 Calcium and Vitamin D3: Diet or Supplements.....	44
6.0 Rehabilitation Therapy.....	54
7.0 Drug Therapy.....	61
8.0 Fracture Management.....	78
Direction for Future Research.....	87
References.....	91
Appendices.....	113
Appendix A: Panel Conflict of Interest Statement.....	113
Appendix B: Search Methodology and Terms Example.....	116
Appendix C: Evidence Tables.....	119
Appendix D: ISCD Position.....	217
Appendix E: Risk of Bias (ROB) Tables.....	234
Appendix F: Putative Fracture Risk Factors.....	241

Preface

This first edition of the Bone Health and Osteoporosis Management in Individuals with Spinal Cord Injury clinical practice guideline (CPG) is the longest and most comprehensive CPG published by the Consortium for Spinal Cord Medicine in its 25 years of existence.

However, do not let the length or apparent complexity and wide breadth of topics covered within this CPG deter you from reading and incorporating the material contained within into your practice, teaching, and patient education. In order to facilitate use, the CPG panel has structured the material into eight different sections, all of which can stand alone, which together provide a comprehensive view of recommended bone health practice and osteoporosis management for persons with spinal cord injury (SCI).

Although a few of the recommendations may be controversial, difficult to implement in the field, and supported by only low-quality evidence, they are all based upon the best possible evidence available, which we hope will align practices and raise awareness of this important but perhaps less visible secondary complication of SCI.

This particular CPG is unique in that it depended on collaboration with the CPG development panel, the International Society of Clinical Densitometry, and the Orthopaedic Trauma Association to align incorporated recommendations acceptable to all.

On behalf of the consortium steering committee, I want first to acknowledge the leadership of the guideline panel, namely, the Chair, Cathy Craven, in guiding this panel through the development process. Next, I would like to commend the panel members themselves for keeping to task and the many reviewers who provided valuable feedback from all areas. All these people, including the panel chair, have volunteered their time to help produce this superb document. In addition, I wish to acknowledge the ongoing support of the Paralyzed Veterans of America, especially President Charles Brown, Executive Director Carl Blake, and Director of Research and Education Cheryl Vines, as well as the rest of the leadership team without whose support these guidelines would not exist.

*Thomas Bryce, MD
Chair, Consortium of Spinal Cord Medicine*

Foreword

This clinical practice guideline (CPG) is intended to aid health care professionals in augmenting bone health and management of osteoporosis among adult individuals living with spinal cord injury/disease (SCI/D). The overall aim of bone health practice and osteoporosis management is to (1) prevent fractures and fracture-related morbidity and mortality and (2) ensure individuals with SCI have an adequate bone mass to allow participation in leisure-time weight-bearing activities without risk of injury.

This guideline contains 8 sections, intended both as stand-alone topics to guide specific members of the interprofessional rehabilitation team and as sections that integrate with one another to provide an overview of comprehensive care from SCI/D onset.

The rich content and diversity of issues covered within this guideline necessitated the input of an interprofessional team and collaboration across multiple organizations and guideline working groups, including the International Society of Clinical Densitometry, the Orthopaedic Trauma Association, and the Consortium for Spinal Cord Medicine. I am grateful for the bootstrapping of the process, leadership, and collegiality of all panel members who worked to align recommendations across organizations with diverse agendas. As panel members, we are grateful for the academic challenge of culling and distilling a large and diverse body of literature.

Sections 1.0-7.0 of the guideline were derived from systematic reviews conducted by the Spinal Cord Injury Research Evidence team and Section 8.0 from a narrative review. Risk of bias diagrams and forest plots are shown throughout the nutraceutical, rehabilitation, and drug therapy sections, where it was feasible to produce them from available published data. It is our intent that these figures serve readers as a visual display of the effect size and potential sources of bias(es) within the literature and the associated guideline recommendations.

We recognize that much of the enclosed recommendations stem from moderate to very low-quality evidence, with a few important exceptions; however, we hope these initial recommendations will serve to align practices and promote cross-site and

cross-country sharing of amalgamated data sets to advance the field in the near term.

During the development of this CPG, several urgent needs for patient education and changes to the curriculum for health care professionals were identified. We trust that you will assist us in escalating and resolving many of these education gaps through sharing of the enclosed recommendations and the consensus positions of partner organizations.

Many research gaps were recognized and highlighted during this guideline process in the hopes that colleagues locally and internationally will work to address the identified research agendas to advance the care of individuals with SCI/D in our lifetime. Successful implementation of this guideline requires health care professionals to partner with individuals with SCI/D and negotiate a joint understanding of their health, bone density results, and risk factors for fracture in order to enable selection of a mutually agreeable treatment plan tailored to the individual's impairments, health preferences, and resources.

We wish to thank Laura Carbone and Fran Weaver for their willingness to support a collaborative process and for providing resources to aid us in gathering deep insights and perspectives during the guideline development process.

Funding support for the development of the inaugural Paralyzed Veterans of America Bone Health and Osteoporosis Management in Individuals with Spinal Cord Injury CPG was provided by funding from Paralyzed Veterans of America, with support from the Department of Defense grant #SCI50092 (L. Carbone, MD), and the Toronto Rehab Foundation (B.C. Craven, MD).

We acknowledge the methodological expertise and scientific contributions of Janice Eng, Matthew Quéré, and the Spinal Cord Injury Research Evidence (SCIRE) team (<https://scireproject.com/>) for conducting the systematic searches, extracting the data, and creating the risk of bias and effect size diagrams shown throughout the prevention and treatment sections of this guideline.

We wish to acknowledge the strong scientific and editorial contributions of William Geerts, MD, University of Toronto; Tomas Cervinka, PhD, PT, Finland; Hardeep Singh, PhD, University of Toronto; and Emily Newton, BA, OT candidate, KITE Research Institute, University Health Network.

We thank Dr. Chris Shuhart, International Society of Clinical Densitometry (ISCD) President, for convening “Bone Mineral Density Testing in Spinal Cord Injury: 2019 ISCD Official Positions” chaired by L. Morse in 2019 and for the ISCD’s willingness to allow the panel’s recommendations to be incorporated in this CPG.

These collaborative processes would not have been possible without the sustained support of Cheryl Vines and Lindsay Perlman throughout the process.

As panel chair, I wish to acknowledge the strong academic contributions, collaborative efforts, and monstrous work ethic of the panel members who demonstrated immense resilience in the face of multiple personal stressors and a global pandemic during the development and refinement of this guideline.

B Catherine Craven, MD
Panel Chair

Acknowledgments

Paralyzed Veterans of America (PVA) is proud to sponsor the development and dissemination of the spinal cord injury (SCI) clinical practice guidelines (CPGs). For over 25 years, we have partnered with the Consortium of Spinal Cord Medicine in a shared mission to improve the health of individuals living with SCI. Today, hundreds of thousands of copies of the guidelines are used around the world by physicians and other medical professionals who provide care to individuals living with SCI at every level, from the emergency department to acute care, rehabilitation to community services.

We sincerely thank Dr. Cathy Craven for bringing this important topic to the Consortium and advocating for its inclusion as a CPG, as well as her leadership and perseverance in guiding this new guideline into practice. Sincere thanks are also extended to each of panel members who worked tirelessly, without remuneration, to bring this project to fruition. PVA was pleased to collaborate with Dr. Frances Weaver and Dr Laura Carbone and their Department of Defense project to support the expansion of the panel and addition of experts for these guidelines.

Chair Dr Thomas Bryce and the members of the SCI Consortium have provided vision, leadership, and support in bringing this and many other CPGs to completion. Their efforts and those of the field reviewers assure the high quality of the recommendations.

This CPG is based on a comprehensive search of the latest evidence. We are grateful to the Spinal Cord Injury Research Evidence (SCIRE) (www.scireproject.com) team for searching, extracting, and grading the literature. Particular thanks go to SCIRE Director Dr. Janice Eng and Research Coordinator Matthew Queree for their exceptional support of the methodology and development of the guidelines.

Within PVA, work on this guideline benefitted from the efforts of many. However, special appreciation goes to graphic designer Charles Swinford and to our medical editor Barbara Every.

Finally, it is only with the significant mission-driven support of PVA, our leadership and our members, that we are able to provide these services. Sincere thanks to PVA President Charles Brown, Past President David Zurfluh, Executive Director Carl Blake, and Deputy Executive Director Shaun Castle.

The Consortium for Spinal Cord Medicine

The Consortium is a collaboration of professional and consumer organizations funded and administered by the Paralyzed Veterans of America (PVA). The Steering Committee, administratively supported by PVA's Research and Education Department, is made up of 1 representative from each Consortium-member organization. The Consortium's mission is to direct the development and dissemination of evidence-based CPGs and companion consumer guides to improve the health care and quality of life for individuals with SCI.

Summary of Guidelines Development Process

The development of these guidelines involved the following major steps: creating a list of formal questions to be addressed, systematic searches of published literature related to these questions, critical appraisal of the quality of the retrieved studies, abstraction of relevant study results, creation of evidence-based recommendations, writing and revising of various drafts of text that explain the recommendations, and multiple reviews by panel members and outside organizations. The Consortium's CPG development process also involved extensive field review and a legal review.

Panel

The first step in any clinical practice guideline is the selection of the panel who will create the guidelines. This is a great effort and commitment on the part of these individuals. The Consortium of Spinal Cord Medicine (CSCM) take the selection of the panel very seriously. Once a topic area is identified, the Consortium does an international search for an expert to lead the panel. The Consortium Chair and PVA Director of Research and Education interview prospective chairs. Interested individuals submit letters of interest and curriculum vitae. Once the Chair has identified a prospective chair, that person, B. Cathy Craven, MD for this document is introduced to the CSCM members and a vote is taken to appoint. Dr Craven was appointed unanimously. The panel chair then selects a panel of experts to serve on the panel. CSCM members make recommendations for individuals in their organizations/fields, but the panel chair makes the final selection of members. Once the panel is identified, their names and credentials are submitted to the CSCM who again vote to ratify the members. Again, the members of this panel were endorsed unanimously. Each panel member completes a Conflict of interest and Confidentiality of Information agreement (see Appendix A)

Panel Members

B. Catharine Craven, BA, MD, MSc

Medical Director, Spinal Cord Injury Program
Lyndhurst Centre, University Health Network
Professor, Division of Physical Medicine and Rehabilitation
Temerty Faculty of Medicine
University of Toronto
Toronto, ON Canada

Anthony S. Burns MD MSc

Brain and Spinal Cord Rehabilitation Program
University Health Network (UHN) – Toronto
Rehabilitation Institute
Professor, Division of Physiatry, Dept. of Medicine
University of Toronto, Toronto, ON Canada

Laura D. Carbone MD, MS

J. Harold Harrison, MD, Distinguished University Chair
in Rheumatology
Professor of Medicine and Division Chief of
Rheumatology
Medical College of Georgia at Augusta University
Staff Physician, Charlie Norwood VA
Augusta, GA

Christopher M. Ciriigliaro, PhD

Investigator
VA RR&D National Center for the Medical
Consequences of Spinal Cord Injury
James J. Peters VA Medical Center
Bronx, NY

Kristine Cowley, PhD

Director, Spinal Cord Research Centre
Associate Professor of Physiology & Pathophysiology
Rady Faculty of Health Sciences
University of Manitoba
Winnipeg, MB, Canada

Janice Eng, PhD, PT

Director of Rehabilitation Research
GF Strong Rehabilitation Hospital
Professor and Research Chair
Department of Physical Therapy
University of British Columbia
Vancouver, BC Canada

Gail Forrest, PhD

Director, Center for Mobility and Rehabilitation
Engineering Research
Tim and Caroline Reynolds Center for Spinal
Stimulation
Kessler Institute for Rehabilitation
West Orange, NJ

Therese E. Johnston, PT, PhD, MBA

Professor
Department of Physical Therapy
Arcadia University
Glenside, PA

B. Jenny Kiratli, PhD

Director, SCI Clinical Research
Spinal Cord Injury and Disorders Center
VA Palo Alto Health Care System
Palo Alto, CA

Sarah Morgan, MD, RD

Professor of Nutrition Sciences and Medicine
Division of Clinical Immunology & Rheumatology
Medical Director, Osteoporosis Prevention and
treatment Clinic,
University of Alabama, Birmingham
Birmingham, AL

Leslie Morse, DO

Department Head and Professor, Department of
Rehabilitation Medicine
University of Minnesota Medical School
Minneapolis, MN

Karen L. Troy, PhD

Professor, Biomedical Engineering
Worcester Polytechnic Institute
Worcester, MA United States

Frances M. Weaver, PhD

Research Health Scientist
Hines VA Hospital
Professor, School of Health Sciences and Public Health
Loyola University
Maywood, IL

Consultants to the Panel

Tomas Cervinka, PhD(tech.), PT

Physiotherapist
Rehabilitation Department,
Hospital Nova, Central Finland Health Care District
University of Jyväskylä
Jyväskylä, Finland

William Geerts, MD

Professor, Department of Medicine
University of Toronto
Director, Thromboembolism Program
Sunnybrook Health Sciences Centre
Toronto, ON

Expert Reviewers

Academy of Spinal Cord Injury Professionals Nurses Section

Lisa Beck MS, APRN, CNS, CRRN
Mayo Clinic
Rochester, MN

Academy of Spinal Cord Injury Professionals Physicians Section

Jeffery Johns, MD
Vanderbilt University Medical Center
Nashville, TN

MaryAnn Richmond, MD
Veterans Administration
Northeast Ohio Healthcare System
Cleveland, OH

Matthew Kubiak, PharmD
Louis Stokes Cleveland VA Medical Center
Cleveland, OH

Binnan Ong, DO
Louis Stokes Cleveland VA Medical Center
Cleveland, OH

American Academy of Neurological Surgeons

J. Adair Prall, MD, FACS, FAAN
AANS/CNS Joint Section for Neurotrauma and Critical Care
Chicago, IL

Gregory Hawryluk, MD, PhD, FRCSC
University of Manitoba
Winnipeg, MB, Canada

American Academy of Physical Medicine and Rehabilitation

David Chen, MD
Shirley Ryan AbilityLab
Chicago, IL

American Occupational Therapy Association

Theresa L. Gregorio-Torres, OTR, MA, ATP
TIRR Memorial Hermann Hospital
Houston, TX

Coleen Zale, MOT, OTR/L, PT, DPT
Shirley Ryan Ability Lab
Chicago, IL

American Physical Therapy Association

Rachel Tappan, PT, DPT
Northwestern University, Feinberg School of Medicine
Chicago, IL

Kristen Hohl, PT, DPT, NCS
Shirley Ryan Ability Lab
Chicago, IL

Casey Kandilakis, PT, DPT
Shepherd Center
Atlanta, GA

American Spinal Injury Association

Gregory Nemunaitis, MD
Cleveland Clinic Foundation
Cleveland, OH

Christina V. Oleson, MD
MetroHealth Medical Center
Cleveland, OH

Department of Veterans Affairs

Stephen Burns, MD
Puget Sound Health Care System
Seattle, WA

Lance Goetz, MD
Hunter Holmes McGuire VAMC
Richmond, VA

Michael Priebe, MD
Charlie Norwood VA Medical Center
Augusta, GA

Kiki Kapolis, PharmD
Portland VA Medical Center
Portland, OR

Doug Ota, MD
Palo Alto VA Healthcare System
Palo Alto, CA

Jelena N. Svircev, MD
Department of Veterans Affairs
Puget Sound Health Care System
Seattle, WA

Wei Han Tan, MD
North Texas Healthcare System
Dallas, TX

International Spinal Cord Society

Thomas Bryce, MD
Icahn School of Medicine at Mount Sinai
New York, NY

Kristjan Ragnarrson, MD
Icahn School of Medicine at
Mount Sinai
New York, NY

Lisa Ruppert, MD
Memorial Sloan Kettering Cancer
Center
New York, New York

Fin Bering Sorenson
Copenhagen University Hospital
Copenhagen, Denmark

PRAXIS

Colleen O’Connell, MD, FRCPC
Praxis Spinal Cord Institute
Vancouver, BC, Canada

Adreane Richard – Denis MD, MSc
Université de Montréal
Montreal, Quebec, CANADA

Christopher Embree, MD, FRCPC,
PM&R
Horizon Health Network
Frederickton, NB, Canada

United Spinal Association

Jane Wierbicky, RN
United Spinal Association
Kew Gardens, NY

Invited Expert Reviewer

William Bauman, MD
James J Peters VAMC
Bronx, New York, NY

Abbreviations

1,25-(OH)₂D .. 1,25-dihydroxyvitamin D	HRpQCT high-resolution peripheral quantitative computed tomography
25-(OH)D 25-hydroxyvitamin D	IgA immunoglobulin A
aBMD areal bone mineral density	ISCD International Society of Clinical Densitometry
ACCP American College of Chest Physicians	IV intravenous
AD autonomic dysreflexia	LC liquid chromatography
AIS American Spinal Injury Association (ASIA) Impairment Scale	LH luteinizing hormone
AIS-A no sensory or motor function preserved	LMWH low molecular weight heparin
AIS-B sensory function preserved below the neurological level of injury	LSC least significant change (95% CI = precision error (RMS-CV) 2.77) (ISCD Position Statement)
AIS-C motor function preserved at the most caudal sacral segments	MGUS monoclonal gammopathy of uncertain significance
AIS-D motor incomplete with at least half of key muscle functions below the single neurological level of injury	MM multiple myeloma
BMC bone mineral content	NMES neuromuscular electrical stimulation
BMD bone mineral density	ntSCI non-traumatic spinal cord injury
BP bisphosphonate	ONJ osteonecrosis of the jaw
BR buckling ratio	OR odds ratio
BSI bone strength index	OTA Orthopaedic Trauma Association
CAROC Canadian Association of Radiologists and Osteoporosis Canada	PEDro Physiotherapy Evidence Database scores used to appraise therapy literature
CI confidence interval	PICOTS Population, Interventions, Comparators, Outcomes, Timing, Setting, Study Design
CKD chronic kidney disease	pQCT peripheral quantitative computed tomography
CPG clinical practice guideline	PT proximal tibia
CSA cross-sectional area	PTE proximal tibia epiphysis
CSI compressive strength index	PTH parathyroid hormone
CT computed tomography	PTM proximal tibia metaphysis
CTz cortical thickness index	PVA Paralyzed Veterans of America
CTX C-terminal telopeptide of type I collagen	QCT quantitative computed tomography
CV coefficient of variation	RANKL receptor activator of nuclear factor kappa B ligand
DF distal femur	RCT randomized controlled trial
DFD distal femur diaphysis	RMS-CV root mean square coefficient of variation
DFE distal femur epiphysis	RMS-CV% root mean square coefficient of variation percent
DFM distal femur metaphysis	ROI region of interest
DOAC direct oral anticoagulant	RR relative risk
DXA dual-energy X-ray absorptiometry	SC subcutaneous
FES functional electrical stimulation	SCI spinal cord injury
FRAX Canadian Fracture Risk Assessment	SCI/D spinal cord injury and disease
FSH follicle-stimulating hormone	SCIRE Spinal Cord Injury Research Evidence
GFR glomerular filtration rate	SD standard deviation
GRADE Grading of Recommendations Assessment, Development and Evaluation	
HR hazard ratio	

SHBG sex hormone-binding globulin
SLOP sublesional osteoporosis
SMD..... standardized mean difference
SSI..... stress strain index
SWAN Study of Women’s Health Across the
Nation

tSCI traumatic spinal cord injury
TSH thyroid-stimulating hormone
vMD..... volumetric bone mineral density
vBMC..... volumetric bone mineral content
VTE venous thromboembolism
ZA zoledronic acid

Glossary of Terms

Active standing refers to a more dynamic condition, when standing involves some muscle activation, either by voluntary muscle contraction (e.g., in people with incomplete spinal cord injury [SCI]) or by using functional electrical stimulation (FES)/neuromuscular electrical stimulation (NMES).

Chronic kidney disease (CKD) is a gradual loss of kidney function. There are five stages of CKD which are classified based on an individual's Glomerular Filtration Rate (GFR) with mild disease beginning with a GFR of 60-90 ml/min and End Stage disease with GFR of <15ml/min.

Fragility fractures are defined in SCI as those that occur after a fall from standing or seated height, or less, or in the absence of trauma such as during routine activities of daily living.

Functional electrical stimulation (FES) refers to the process of pairing NMES simultaneously or intermittently with a functional task, such as cycling or rowing.

Hypercalciuria has been defined as a 24-hour urinary calcium excretion greater than 275 mg in men and greater than 250 mg in women, although this does not take into account urinary concentration, renal function, or weight.

Menopause is defined as the absence of menses for 12 consecutive months with no other biological or physiological cause identified.

Neuromuscular electrical stimulation (NMES) is defined as the application of an electrical current of sufficient intensity to elicit muscle contraction.

Passive standing may be performed with individuals with motor complete SCI in a standing frame, standing wheelchair, long leg braces, or other devices.

Prevention is defined as intervention prior to the development of low bone mineral density (BMD) and increased fracture risk.

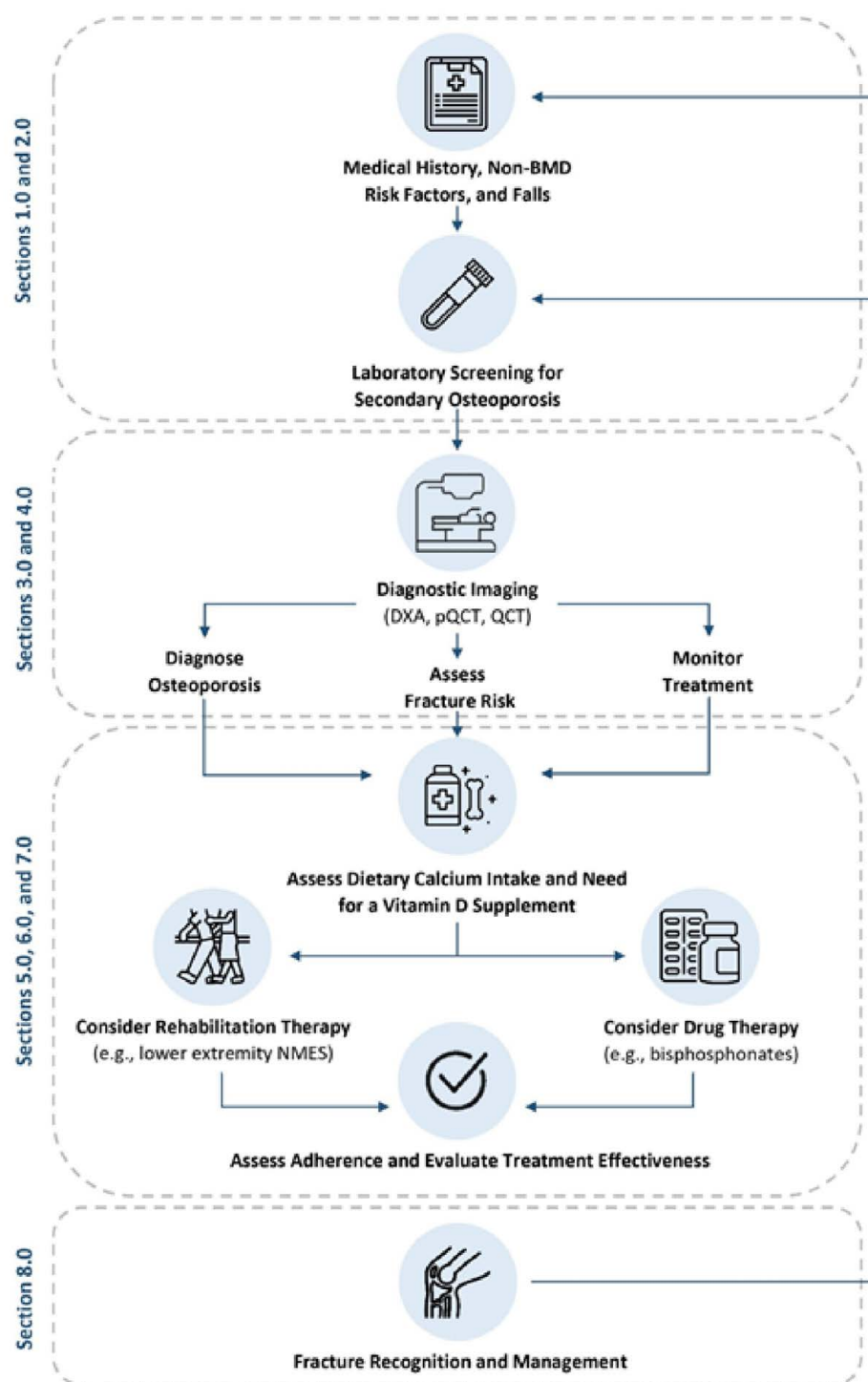
Spinal Cord Injury/Disease (SCI/D): Non-traumatic SCI are diseases affecting the spinal cord also called SCI/D throughout this guideline. SCI/D are typically caused by spondylosis or degeneration of the spine compressing the cord, compression of the cord by a tumor, loss of cord blood supply due to vascular ischemia, infectious disease or abscesses and transverse myelitis.

Treatment is defined as an intervention in the context of established low BMD and increased fracture risk.

Clinicians Guide to the Clinical Practice Guideline

This Bone Health and Osteoporosis Management clinical practice guideline (CPG) includes a number of diverse topics that will be relevant to many members of the interprofessional rehabilitation team when providing bone health services to individuals with spinal cord injury/disease (SCI/D). The figure illustrates how the concepts introduced throughout the guideline relate to one another and form a preliminary care map for individuals with SCI/D. The figure displays a sequential process for bone health and osteoporosis management care. This process should be initiated early after injury, but is also appropriate for those with chronic SCI, or any time after an individual sustains a fracture. The panel members recognize that not all sections of the CPG will be relevant to every clinician.

Clinicians are encouraged to familiarize themselves with the flow diagram and to select the sections most pertinent to their practice for review and implementation. For example, we anticipate that physicians and clinicians interested in bone health screening may find Sections 1.0, 2.0, 3.0, and 7.0 most relevant; dietitians may find Sections 2.0 and 5.0 most relevant; physical therapists may find Sections 6.0 and 8.0 most relevant; occupational therapists may find Sections 1.0 and 8.0 most relevant; radiologists, densitometrists, and bone health scientists will find Sections 3.0 and 4.0 of interest; and pharmacists will find Sections 5.0, 7.0, and 8.0 most relevant. We ask that readers recognize that the entire CPG is intended to vividly illustrate core bone health assessments and interventions; however, each section may act as a stand-alone resource when used in combination with the corresponding references and appendices.



Executive Summary of the Recommendations

1.0 Medical History, Assessment of Fracture and Fall Risk

- 1.1 We recommend that clinicians routinely assess fracture risk at least on an annual basis.
1B
- 1.2 We recommend that clinicians assess non-bone mineral density (BMD) risk factors for fracture following a change in functional abilities, minor injury after a fall, or a fragility fracture (see risk factor checklist in Table 1.2).
1B
- 1.3 We recommend that clinicians use hip, distal femur, and proximal tibia region BMD and prior history of fracture as the primary considerations for predicting lower extremity regional fracture risk.
1B
- 1.4 We recommend that clinicians routinely assess an individual's fall risk.
1A
- 1.5 We recommend that following an injurious fall, clinicians offer individuals with SCI fall prevention education, transfer/wheelchair skills upgrading, and/or balance training to reduce the risk of falls and increase their confidence in community participation.
1D
- 1.6 We suggest that, after a fall, clinicians reassess the individual's level of confidence in navigating their home and community environments with a view to mitigate future fall risk and/or fragility fracture.
2C
- 1.7 SCI rehabilitation programs may consider establishing SCI-specific fall prevention programs accessible to individuals with SCI across the continuum of care.
2D

2.0 Laboratory Screening

- 2.1 We recommend that, in the context of bone health screening, all adult women and men with spinal cord injury (SCI), regardless of injury duration, should have measurements of serum 25-hydroxyvitamin D (25-(OH)D) done by a validated assay method; complete blood cell count; ionized calcium (or calcium adjusted for albumin), phosphate, intact parathyroid hormone, creatinine (and estimated glomerular filtration rate), bone-specific alkaline phosphatase and transaminases, hemoglobin A1C, and thyroid-stimulating hormone levels; and 24-hour urine collection for calcium and creatinine excretion.
1C
- 2.2 We recommend that premenopausal adult women with SCI have the laboratory tests listed in 2.1, with additional measurements of prolactin, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol levels.
1D
- 2.3 We recommend that adult men with SCI have the laboratory tests listed in 2.1, with additional measurements of LH, FSH, and morning fasting serum bioavailable testosterone levels.
1D
- 2.4 One may consider protein electrophoresis in individuals over 50 years of age or individuals who present with a vertebral compression fracture of unknown etiology.
2D

- 2.5 One may consider the following additional testing if clinically indicated:
- 24-hour urinary cortisol/overnight dexamethasone suppression test if Cushing's disease is suspected
 - anti-tissue transglutaminase immunoglobulin A antibody if celiac disease is suspected

2D

3.0 Bone Density Testing with Dual-Energy X-ray Absorptiometry

- 3.1 We recommend that clinicians adhere to the 2019 ISCD Adult Official Positions for DXA in Patients with Spinal Cord Injury.

1B

- 3.2 All adults with spinal cord injury resulting in permanent motor or sensory dysfunction should have a DXA scan of the total hip, proximal tibia, and distal femur as soon as medically stable.

1A

- 3.3 In adults with SCI, total hip, distal femur and proximal tibia bone density should be used to diagnose osteoporosis, predict lower extremity fracture risk and monitor response to therapy where normative data are available.

1B

- 3.4 Serial DXA assessment of treatment effectiveness among individuals with SCI should include evaluation at the total hip, distal femur, and proximal tibia, following a minimum of 12 months of therapy at 1- to 2-yr intervals. Segmental analysis of total hip, distal femur and proximal tibia sub-regions from a whole-body scan should not be used for monitoring treatment.

1B

- 3.5 There is no established threshold BMD value below which weight-bearing activities are absolutely contraindicated. BMD and clinical risk factors should be used to assess fracture risk prior to engaging in weight-bearing activities.

1B

4.0 Volumetric Bone Density and Bone Architecture: Peripheral Quantitative Computed Tomography and Quantitative Computed Tomography

- 4.1 We recommend that, as an alternative to DXA, peripheral quantitative computed tomography (pQCT) or quantitative computed tomography (QCT) imaging of the lower extremity can be used for monitoring bone health in adults with SCI.

1B

- 4.2 We recommend that both trabecular and cortical sites of the femur and tibia be measured annually to monitor regional changes in bone density and quality.

1B

- 4.3 We recommend that QCT of the hip can be used for diagnosing osteoporosis among individuals with SCI in accordance with International Society of Clinical Densitometry (ISCD) guidelines.

1B

- 4.4 We recommend the following anatomical sites for pQCT measurement for individuals with SCI where feasible, moving from distal to proximal starting from a reference line placed at the talocrural joint (4% tibia) to the distal end of the lateral femoral condyle (4% femur): measurements at the tibia 4%, 38%, 66%; measurement at the femur 4%.

1B

- 4.5** We recommend the following anatomical sites for QCT measurement among individuals with SCI: proximal femur, distal femur, proximal tibia. It is essential that QCT regions of interest be clearly defined and reported according to published best practices and guidelines.

1B

- 4.6** We recommend that at a minimum the following metrics should be reported from pQCT:
- For trabecular sites (4% tibia and 4% femur): integral (also termed “total”) and trabecular volumetric bone mineral density (vBMD), cross-sectional area (CSA), and bone mineral content (BMC). If available, bone strength index (BSI) should be reported.
 - For cortical sites (38% and 66% tibia): BMC and CSA.

1B

- 4.7** We recommend that at a minimum, the following metrics should be reported from QCT: integral, cortical, and trabecular vBMD, BMC, CSA, and cortical thickness.

1A

- 4.8** We recommend that monitoring be performed when expected changes are greater than the individual least significant change of the measurement method. For general monitoring, measurements may be performed annually. Because cortical or trabecular compartments may change somewhat independently, it is important to monitor multiple sites (see 4.4 and 4.5) and to assess and report measurement precision.

1A

- 4.9** We recommend that measurement precision be assessed and reported for each outcome metric as root mean square coefficient of variation (RMS-CV).

1A

5.0 Calcium and Vitamin D3: Diet or Supplements

- 5.1** We recommend that 25-hydroxyvitamin D (25-(OH)D) levels be repleted at least to a level of 80 nmol/L (32 ng/mL) in individuals with SCI and that maintenance doses of vitamin D3 (cholecalciferol) of 25-50 mcg/day (1,000-2,000 IU/day) are reasonable in the SCI population. 25-(OH)D levels should be checked annually and 12 weeks following repletion therapy with a validated assay.

1B

- 5.2** The following are recommendations for calcium intake as a combination of food and supplements (preference for dietary intake over supplements):

Group and Age Calcium Recommendation

Men and premenopausal women age 19-50 years..... 1,000 mg/day
Men 50-70 years 1,000 mg/day
Women 50-70 years 1,000-1,200 mg/day
Men and women 71+ years..... 1,000-1,200 mg/day
*Not appropriate for individuals who are found to be hypercalcemic.

1B

- 5.3** One may consider a calcium intake of 750-1,000 mg/day from food and supplements for individuals with SCI and calcium oxalate stones, with a preference for dietary intake over supplements.

2D

6.0 Rehabilitation Therapy

- 6.1** One may consider passive standing for 1 hour 5 times per week for at least 2 years to reduce BMD decline at the hip and knee regions.

2D

- 6.2** We suggest lower extremity functional electrical stimulation (FES) or neuromuscular electrical stimulation (NMES) as an option for preventing BMD decline in the hip and knee region. The most effective FES and NMES interventions should include the following:

6.2.1 We recommend that FES delivery create a visibly strong contraction against some resistance during some functional task, such as cycling or rowing, using appropriate stimulation parameters to create lower limb muscle contractions (e.g., pulse durations of 200 μ s or higher, frequencies of 20-33 Hz, and amplitudes up to 140 mA), for at least 30 minutes, 3-5 days per week, for at least 1 year.

1D

6.2.2 We recommend that NMES delivery create a visibly strong contraction against some resistance, such as an isometric contraction or movement against gravity or during loading, using appropriate stimulation parameters to create lower limb muscle contractions (e.g., pulse durations of 200 μ s or higher, frequencies of 20-33 Hz, and amplitudes up to 140 mA, but the effective stimulation parameters may vary among individuals), for at least 30 minutes, 3-5 days per week, for at least 1 year.

1B

- 6.3** We suggest lower extremity FES or NMES as an option for treating low BMD in the lower limbs. The most effective FES and NMES interventions should include the following:

6.3.1 We recommend that NMES delivery create a visibly strong contraction against incrementally increasing resistance, such as an isometric contraction or movement against gravity or during weight bearing, using appropriate stimulation parameters to create lower limb muscle contractions (e.g., pulse durations of 200 μ s or higher, frequencies of 20-33 Hz, and amplitudes up to 140 mA have been reported, but effective stimulation parameters may vary among individuals), for at least 30 minutes, 3-5 days per week, for at least 1 year.

1B

6.3.2 We recommend that FES delivery create a visibly strong contraction against incrementally increasing resistance, using appropriate stimulation parameters to perform some functional task (e.g., pulse durations of 200 μ s or higher, frequencies of 20-33 Hz, and amplitudes up to 140 mA have been reported, but effective stimulation parameters may vary among individuals), for at least 30 minutes, 3-5 days per week, for at least 1 year.

1D

- 6.4** We suggest that a minimum duration of 1 year for lower extremity muscle-activated and load-bearing rehabilitation therapy is needed before an effect on bone density is expected. Further, to maintain effects on bone density, lower extremity muscle-activated and load-bearing rehabilitation therapy needs to be continued indefinitely.

1B

7.0 Drug Therapy

- 7.1** We recommend that clinicians and individuals with SCI use a shared decision-making process that accounts for patients' values, preferences, and comorbidities when selecting therapy and avoiding adverse effects.
1C
- 7.2** We recommend, given the anticipated declines in hip and knee region areal bone mineral density (aBMD) during the first 12-18 months after injury, that a discussion of the risk-benefit ratio of currently available drug therapy occur with individuals with acute SCI who are anticipated to be primary wheelchair users.
1C
- 7.3** We recommend the administration of alendronate, zoledronic acid, or denosumab if, after discussion with the individual, there is a desire to prevent secondary bone mineral loss, taking into account the potential risk-benefit ratio.
1C
- 7.4** We recommend that individuals with SCI, low bone mass, and moderate-to-high fracture risk be offered oral alendronate, intravenous zoledronic acid, or subcutaneous denosumab combined with adequate calcium and vitamin D3 (see Section 5.0) to treat low total hip, distal femur, or proximal tibia aBMD.
1B
- 7.5** We recommend that clinicians use the least significant change (LSC) to assess true biological change over time, defined as bone gain or bone loss that exceeds the LSC.
1A
- 7.6** We suggest that clinicians reassess (stop, continue, or change) osteoporosis therapies if significant bone loss occurs for 2 consecutive years despite good adherence.
2C
- 7.7** We suggest that clinicians reassess (stop, continue, or change) osteoporosis therapies if a long bone fragility fracture occurs in an individual with SCI who has been adherent to therapy for more than 1 year.
1D
- 7.8** One may consider initiating a drug holiday for individuals with moderate fracture risk following 5 years of consecutive treatment with oral bisphosphonate therapy or 3 years of intravenous bisphosphonate therapy.
2D
- 7.9** One may consider, for individuals with high and very high fracture risk or prior fracture, a treatment duration of 7-10 years for oral bisphosphonates or 6 annual doses of intravenous zoledronic acid.
2D
- 7.10** One may consider trialing an alternative intervention if side effects or poor adherence preclude continued therapy.
2D

8.0 Fracture Management

- 8.1** We recommend that individuals with SCI and lower extremity long bone fragility or traumatic fracture undergo an orthopedic consultation.
1D
- 8.2** We recommend that clinicians actively identify individuals with SCI and a lower extremity fracture as having a diagnosis of osteoporosis, and be treated as having a moderate-to-high fragility fracture risk.
1B
- 8.3** One may use shared decision making to weigh the risks and benefits of surgical or conservative fracture management that accounts for the patients' values, preferences, health status, medical comorbidities, and available post-fracture attendant care resources.
2D
- 8.4** We recommend that, when conservative fracture management is selected, clinicians prescribe soft, custom-molded, immobilization devices; bivalve the device; and provide heel and malleolar windows to prevent regional skin breakdown.
1D
- 8.5** We recommend that clinicians proactively assess the presence of leg edema and risk of skin injury and use multilayered compression wraps to help mitigate edema in individuals at risk.
1D
- 8.6** We recommend that clinicians prescribing immobilization devices to wheelchair users with SCI/D and lower extremity fracture consider prescribing an elevating leg rest and/or additional attendant care supports.
1D
- 8.7** We recommend, for individuals with chronic SCI who develop a new hip, femur, or tibia fracture, that clinicians routinely assess their risk of venous thromboembolism.
1C
- 8.8** We recommend, for individuals with chronic SCI who develop a new hip, femur, or tibia fracture, that clinicians routinely provide anticoagulant thromboprophylaxis with low molecular weight heparin (LMWH) or a direct oral anticoagulant (DOAC) if there are no contraindications
1C
- or*
- Obtain the advice of a health professional with expertise in the area of thromboprophylaxis, such as a SCI rehabilitation physician, hematologist, thrombosis specialist, or internist.
1D
- 8.9** We recommend, for individuals with chronic SCI who develop a new hip, femur, or tibia fracture, that thromboprophylaxis start as soon after the fracture as is feasible.
1C
- 8.10** One may consider, for individuals with chronic SCI who develop a new hip, femur, or tibia fracture who are admitted to hospital, that thromboprophylaxis continue at least until discharge from acute care and rehabilitation with consideration of at least 2-4 weeks.
2D
- 8.11** One may consider, for individuals with chronic SCI who develop a new hip, femur, or tibia fracture who are not admitted to hospital, that thromboprophylaxis continue for at least 2-4 weeks.
2D

8.12 We recommend that clinicians monitor individuals with a neurological level of T6 or above and a recent lower extremity fracture for symptoms of autonomic dysreflexia (AD).

1D

8.13 We recommend that in individuals with persisting AD symptoms and elevated blood pressure at or above 150 mmHg systolic prior to catheterization, clinicians consider rapid-onset and short-duration pharmacological management to reduce the systolic blood pressure without causing hypotension.

1D

8.14 We recommend that individuals with persisting AD symptoms who are not responding to removal of an identified noxious stimulus be transferred to a monitored setting where oral, topical, or intravenous medications (nitroglycerin, hydralazine, or nifedipine) can be administered to acutely lower their systolic blood pressure.¹

1D

8.15 We recommend, for those at risk for AD, that clinicians provide analgesia for nociceptive pain to prevent AD in the first 3-5 days after fracture and implement definitive fracture management.

1D

8.16 One may consider initiation of osteoporosis treatment soon after fragility fracture (see Sections 5.0, 6.0, and 7.0).

2D

8.17 We recommend that following fracture healing, clinicians refer individuals with SCI for a comprehensive mobility assessment that includes transfer training, wheelchair skills upgrading and reconditioning, and bracing/orthotic assessment, as appropriate (see Section 1.0).

1D

8.18 We recommend that clinicians aim to return individuals with SCI to their premorbid hip, knee, and ankle range of motion after fracture healing.

1D

8.19 One may consider that decisions to progress to weight bearing and loading be jointly planned between the treating health care professionals (e.g., orthopedic surgeon, physiatrist, physical therapist) and the individuals with SCI who have a recent fracture in order to reduce the risk of further injury proximal or distal to the fracture site.

2D

8.20 We recommend that clinicians refer individuals with SCI who are wheelchair users with changes in pelvic or lower extremity alignment, residual deformity, limb length discrepancy, or seating posture after a fracture for a seating reassessment.

1D

8.21 One may consider referring individuals with SCI who are ambulatory with changes in pelvic or lower extremity alignment, residual deformity, or limb length after a fracture for a bracing/orthotic assessment.

2D

Methods

Review of Literature

Preamble

This section contains a summary of the scientific methods used in the development of this clinical practice guideline (CPG). Methodological support by the Spinal Cord Injury Research Evidence (SCIRE) team was provided throughout the CPG development process. A detailed description of the key questions identified by the panel prior to guideline development, the associated literature search, study selection criteria, and reporting process are described herein. The Cochrane risk of bias tool and effect size diagrams were used, where applicable, to inform decision making while synthesizing data, developing recommendations, and formulating a GRADE (Grading

of Recommendations Assessment, Development and Evaluation) recommendation. Exceptions to the described methods in Sections 3.0, 8.0, and 9.0 are noted.

Key Questions

Members of the Bone Health and Osteoporosis Management Clinical Expert Panel formulated key questions (to guide the literature search and study inclusion) related to prevalence, assessment, and treatment of bone health in the spinal cord injury (SCI) population. Key questions generated by this panel, in addition to other questions that arose as the literature was extracted, are listed in Table A.

Table A. Key Questions and Corresponding Guideline Sections

Content Area	Key Question	Section Number
Guidelines	What is the appropriate laboratory screening for secondary causes of osteoporosis in the initial assessment of adults with spinal cord injury (SCI)?	1
Risk factors	What are the non-bone mineral density risk factor(s) for lower extremity fragility fracture in adults with SCI?	2
pQCT validity	As an alternative to dual-energy X-ray absorptiometry (DXA), can peripheral quantitative computed tomography (pQCT) and QCT imaging of the lower extremity be used for diagnosing osteoporosis among adults with SCI?	4
	As an alternate to DXA, can pQCT and QCT imaging of the lower extremity be used for monitoring therapy among adults with SCI?	4
	As an alternate to DXA, at what precision can pQCT be used for monitoring bone health among adults with SCI?	4
DXA anatomical sites	Is there a hierarchy of anatomical sites by DXA to facilitate longitudinal monitoring/ response to therapy in adults with SCI?	3
Nutraceuticals	How do we define ineffective dietary supplements for individuals with low bone mass and traumatic spinal cord injury (tSCI)?	5
	What is the role of dietary calcium, vitamin D, magnesium, protein, and supplements alone or in combination for preventing bone loss or treating osteoporosis?	5

Content Area	Key Question	Section Number
Prevention - Rehabilitation	What is the appropriate use of standing/walking to prevent low bone mass or osteoporosis among adults after SCI?	6
	What is the appropriate use of treadmill training to prevent low bone mass or osteoporosis among adults after SCI?	6
	What is the appropriate use of neuromuscular electrical stimulation (NMES) to prevent low bone mass or osteoporosis among adults after SCI?	6
	What is the appropriate use of functional electrical stimulation (FES) to prevent low bone mass or osteoporosis among adults after SCI?	6
	What is the appropriate use of electrical stimulation to prevent low bone mass or osteoporosis among adults after SCI?	6
	What is the appropriate use of ultrasound to prevent low bone mass or osteoporosis among adults after SCI?	6
	What is the appropriate use of combination therapy to prevent low bone mass or osteoporosis among adults after SCI?	6
Treatment - Rehabilitation	What is the appropriate use of standing/walking to treat low bone mass or osteoporosis among adults after SCI?	6
	What is the appropriate use of physical exercise to treat low bone mass or osteoporosis among adults after SCI?	6
	What is the appropriate use of treadmill training to treat low bone mass or osteoporosis among adults after SCI?	6
	What is the appropriate use of NMES to treat low bone mass or osteoporosis among adults after SCI?	6
	What is the appropriate use of FES to treat low bone mass or osteoporosis among adults after SCI?	6
	What is the appropriate use of vibration to treat low bone mass or osteoporosis among adults after SCI?	6
	What is the appropriate use of electrical stimulation to treat low bone mass or osteoporosis among adults after SCI?	6
	What is the appropriate use of combination therapy to treat low bone mass or osteoporosis among adults after SCI?	6
Prevention - Drug	What is the appropriate use of alendronate to prevent low bone mass or osteoporosis among adults after SCI?	7
	What is the appropriate use of clodronate to prevent low bone mass or osteoporosis among adults after SCI?	7
	What is the appropriate use of etidronate to prevent low bone mass or osteoporosis among adults after SCI?	7
	What is the appropriate use of pamidronate to prevent low bone mass or osteoporosis among adults after SCI?	7
	What is the appropriate use of tiludronate to prevent low bone mass or osteoporosis among adults after SCI?	7
	What is the appropriate use of zoledronic acid to prevent low bone mass or osteoporosis among adults after SCI?	7

Content Area	Key Question	Section Number
Treatment - Drug	What is the appropriate use of alendronate to treat low bone mass or osteoporosis among adults after SCI?	7
	What is the appropriate use of denosumab to treat low bone mass or osteoporosis among adults after SCI?	7
	What is the appropriate use of teriparatide to treat low bone mass or osteoporosis among adults after SCI?	7
	What is the appropriate use of zoledronic acid to treat low bone mass or osteoporosis among adults after SCI?	7
Side effects - Drug	How do we define ineffective alendronate therapy for individuals with low bone mass and tSCI?	7
	How do we define ineffective pamidronate therapy for individuals with low bone mass and tSCI?	7
	How do we define ineffective tiludronate therapy for individuals with low bone mass and tSCI?	7
	How do we define ineffective teriparatide therapy for individuals with low bone mass and tSCI?	7
	How do we define ineffective zoledronic acid therapy for individuals with low bone mass and tSCI?	7
Side effects - Rehabilitation	How do we define ineffective standing/walking therapy for individuals with low bone mass and tSCI?	n/a
	How do we define ineffective treadmill training for individuals with low bone mass and tSCI?	n/a
	How do we define ineffective FES therapy for individuals with low bone mass and tSCI?	n/a
	How do we define ineffective vibration therapy for individuals with low bone mass and tSCI?	n/a
	How do we define ineffective combination therapy for individuals with low bone mass and tSCI?	n/a
Fracture management	After lower extremity fracture, what are the special considerations for the management of adult individuals with SCI?	8

Abbreviation: n/a, not applicable. Indicates topics that were not specifically addressed in the final data synthesis, but are touched on in Section 6.0.

Population, Interventions, Comparators, Outcomes, Timing, Setting, Study Design (PICOTS)

The PICOTS framework was used to develop literature search strategies and to frame and answer a clinical or health care-related question in evidence-based practice.² The PICOTS indicators that we searched for and found include the following:

Population

Adults (18 years and older) with non-acute traumatic spinal cord injury/ disease/disorder/dysfunction (SCI/D) resulting in paralysis (excluding patients with spinal stroke). In studies with mixed populations, at least 20% of the sample needed to include participants with SCI.

Interventions

- Screening, assessment, or outcome measures
 - ☐ Peripheral quantitative computed tomography
 - ☐ Dual-energy X-ray absorptiometry analysis
- Prevention
 - ☐ Alendronate
 - ☐ Clodronate
 - ☐ Etidronate
 - ☐ Pamidronate
 - ☐ Tiludronate
 - ☐ Zoledronate
 - ☐ Standing/Walking
 - ☐ Treadmill training
 - ☐ Neuromuscular electrical stimulation (NMES)
 - ☐ Functional electrical stimulation (FES)
 - ☐ Electrical stimulation
 - ☐ Ultrasound
 - ☐ Combination therapy
- Treatment
 - ☐ Alendronate
 - ☐ Denosumab
 - ☐ Teriparatide
 - ☐ Zoledronate
 - ☐ Standing/Walking
 - ☐ Physical exercise
 - ☐ Treadmill training
 - ☐ NMES

- ☐ FES
- ☐ Vibration
- ☐ Electrical stimulation
- ☐ Combination therapy

Comparators

- Adults without SCI or matched controls (individuals of the same age, gender, physical characteristics)
- Adults with other neurological dysfunction (e.g., amyotrophic lateral sclerosis, multiple sclerosis, spina bifida)
- Another included intervention (head-to-head study in SCI population)
- Usual care
- Placebo
- Outcomes

Osteoporotic status

- Bone mineral density
- Bone fractures
- Setting

Timing

The term of the drug intervention was at least 6 months. Timing or duration of bone health was measured in a variety of intervals (days, weeks, months). Some studies measured participant recall of bone health over the past weeks, months, or year.

Setting

Outpatient and in the community

Study Design

Study designs included randomized controlled trials (RCTs), matched controlled trials, crossover trials, prospective controlled trials, cohort studies, longitudinal studies, case-control studies, pre-post designs, observational and cross-sectional studies, and surveys. Qualitative studies and case reports with at least 3 participants (n=3) were considered for inclusion only if no other credible information existed.

Literature Review

Members of the SCIRE (www.scireproject.com) team comprised the methodology team. They searched Ovid MEDLINE, EMBASE, CINAHL, and PsycINFO from 1980 through June 2019, using search terms related to bone health (e.g., osteoporosis, fracture, bone mineral density), SCI (e.g., paraplegia, tetraplegia, spinal cord injury/disease/disorder/dysfunction), and the topics of inquiry (e.g., assessment, prevalence, treatment). The methodology team also searched the Cochrane Database of Systematic Reviews and Google Scholar for additional studies, systematic reviews, and guidelines in the area of bone health after SCI. The methodology team and panel members identified additional studies through hand searching of the reference lists of included studies and reviews (see Appendix B for example of search strategies and final search numbers: hits, exclusions, and included studies). In select sections, additional articles published between June 2019 and June 2020 were added to the data set by the panel members. The number of hand-searched articles and those added by panel members are shown as a combined number in the PRISMA flow diagram (Figure C).

Study Selection

Study selection was based on the inclusion criteria created in consultation with the Paralyzed Veterans of America (PVA) Bone Health and Osteoporosis Management Guideline Clinical Expert Panel. Two reviewers independently assessed titles and abstracts of citations identified through literature searches by using the inclusion criteria specified below.

Full-text articles of potentially relevant citations were retrieved and assessed for inclusion by both reviewers. Disagreements were resolved by consensus. Review articles were included only if bone health was the focus of discussion and it was a systematic review, meaning that it was designed to find articles that described studies of bone health after SCI, rather than current opinions or research in the area (e.g., in a book chapter).

Study inclusion was guided by 2 key principles: (1) The population of interest had to be individuals with SCI; and (2) the study measured specific outcomes related to bone, osteoporosis, bone mineral density (BMD), or fractures.

The panel requested some customizations of the inclusion criteria as follows:

- Interventions had to be at least 6 months long and to include a minimum of 3 individuals with SCI.
- The focus had to be the following key bone sites: proximal tibia, distal femur, femoral neck, and/or total hip.
- In assessing peripheral quantitative computed tomography (pQCT) validity, only studies that compared dual-energy X-ray absorptiometry (DXA) and pQCT results could be included (construct validity).
- In Section 8, studies were included if they reported side effects (i.e., studies that stated that they “monitored” side effects and/or “nothing happened” were not included) or were pertinent to the discussion.
- Results published only in abstract form or in conference proceedings could be included if adequate details were available for quality assessment (e.g., risk of bias) and if the area of inquiry had relatively little published information, and so the unpublished study would be making a contribution to the field.
- Mixed populations were acceptable if at least 20% of the sample consisted of individuals with SCI/D.

All articles were limited to English only. Animal studies, articles that described only the neurophysiology of bone, and studies that reviewed pediatric human populations were excluded.

Data Extraction

We extracted information from included studies on population characteristics and demographics, interventions, prevalence, measurement, outcomes, and any adverse effects reported. Data abstraction was performed by one reviewer and independently

checked by a second reviewer; any differences were resolved by discussion and/or involving a third reviewer. The data extraction forms were used to compile information from the approximately 135 articles found in the primary and secondary searches. Extracted information was compiled into evidence tables according to subject area and by panel key question (e.g., treatment or prevention, pharmacological or rehabilitation).

Consultation Process

The identified relevant articles and evidence tables were sent to the expert panel for review to study while constructing the CPGs. Subsequently, the SCIRE team responded to queries for additional studies from the panel chair and panel members. Supplemental evidence tables and text were created and included in the final documents to address the additional areas requested.

Data Synthesis

We constructed evidence tables that show the study characteristics, outcomes, and risk of bias for all included studies. A quality assessment of RCTs was performed by using the Physiotherapy Evidence Database (PEDro) scale (www.pedro.org.au). Generally, RCTs with a score of <4 are considered to be poor quality, those with scores of 4-5 fair quality, those with scores of 6-8 good quality, and those with scores of 9-10 excellent quality.³ We presented the studies to the panel members by using a hierarchy-of-evidence approach, where the best evidence was presented first in the tables and is the focus of any results, point estimates, or conclusions. The panel members chose to present the results in alphabetical order to facilitate readers' ease in locating the evidence (see Appendix C). In some instances, intervention data was not considered in the formulation of recommendations if the drug or device is no longer available or no longer manufactured. The removal of relevant data is reported and the rationale for removing it when formulating recommendations is specified within the text of each section.

Validity Assessment (Risk of Bias)

We assessed the risk of bias for intervention studies (Sections 5.0, 6.0, and 7.0) by using the Cochrane risk of bias tool⁴; the risk of bias figures for these studies are shown in Appendix C. We assessed the internal validity (risk of bias) of trials, observational studies,

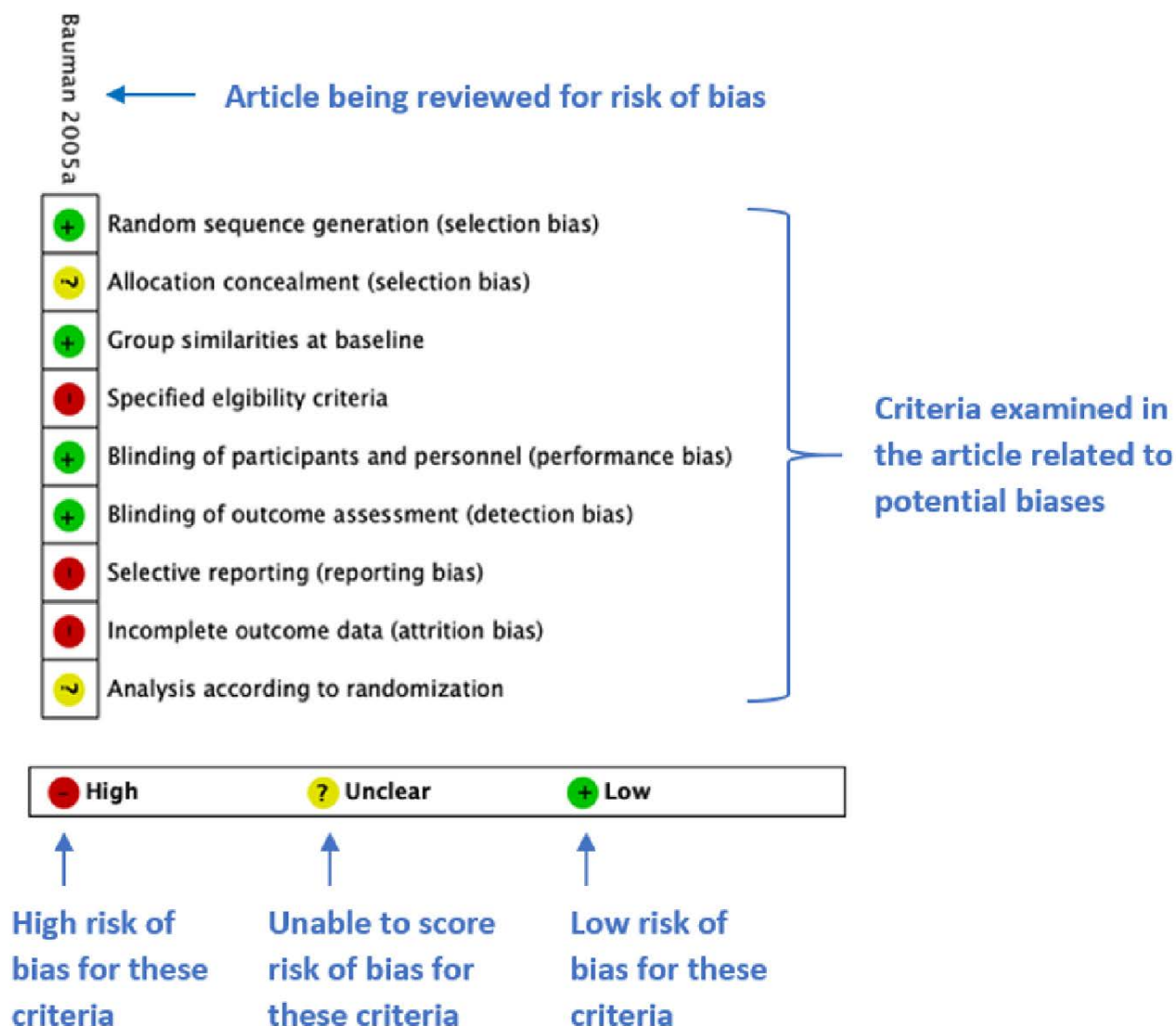
and systematic reviews on the basis of the methods used for randomization, allocation concealment, and blinding; similarity of compared groups at baseline; loss to follow-up; and accounting for any statistical confounds. The results were then accumulated to assess the trials as high, moderate, or low risk of bias. Studies with a high attrition rate (e.g., 15% or greater) or a low response rate (lower than 50%) were automatically rated as a high risk of bias.

Observational studies were rated on non-biased selection, loss to follow-up, pre-specification of outcomes, well-described and adequate ascertainment techniques, statistical analysis of potential confounders, and adequate duration of follow-up.

Systematic reviews were rated on clarity of review question, specification of inclusion and exclusion criteria, use of multiple databases for searching, sufficient detail of included studies, adequate assessment of risk of bias of included studies, and provision of an adequate summary of primary studies.

Two reviewers independently assessed the quality of each study, and differences were resolved by discussion to reach consensus. Risk of bias summary figures provide a visual representation of the risk of bias ratings (Figure A).

Figure A. Components of a risk of bias summary figure, in which the Cochrane risk of bias tool was used to create it⁴ (see Appendix C, which contain the risk of bias figures).



Grading the Quality of Evidence

We assessed the quality of evidence by using the PEDro scale and a risk of bias assessment. The PEDro scale provides a system for rating the strength and quality of evidence from clinical trials; it consists of a checklist of 10 scored yes-or-no questions related to the internal validity and statistical information provided. A high PEDro score correlates to high quality of evidence reported by a particular study. The risk of bias assessment depicts systematic flaws or limitations in a study's design, conduct, or analysis, which should lower confidence in the study's reported findings.

Effect Size Diagrams and Forest Plots

Effect Size

The effect size is the magnitude of a treatment effect (e.g., a specific intervention) or the strength of an association between 2 variables.⁵ In a meta-analysis, the effect size from each included study is computed and compared across all of the included studies to assess consistency (homogeneity) and overall effect.⁶ Furthermore, the effect measure is defined by the type of data: dichotomous, continuous, ordinal or scales, counts and rates, and time-to-event (survival) outcomes.⁷

For instance, there are various indices of effect sizes to capture between-group differences such as the standardized mean difference (e.g., Cohen's *d*, Hedges' *g*); dichotomous outcomes that are measured by odds ratio, relative risk, or risk ratio; or measure of associations such as Pearson's correlation or coefficient of determination.⁸ In a meta-analysis, the effect sizes are summarized in a forest plot that is used for pooled estimates and consistency evaluations. Although no meta-analyses were conducted, forest plots were used to show standard mean differences. Throughout this CPG, Hedges' *g*, a variation of Cohen's *d*, was used to correct for potential biases related to small sample sizes.

Forest Plots

Forest plots display the estimated results from a study or number of studies that address the same question and allow the reader to see the overall results (figure).

Interpretation

Two main aspects of a forest plot are of importance: heterogeneity and overall effect (pooled or combined) result. Heterogeneity tests for overall consistency of the effect sizes between included studies. Most statistical packages for meta-analysis report this value and its representative *p*-value that is used for conclusions regarding the heterogeneity or

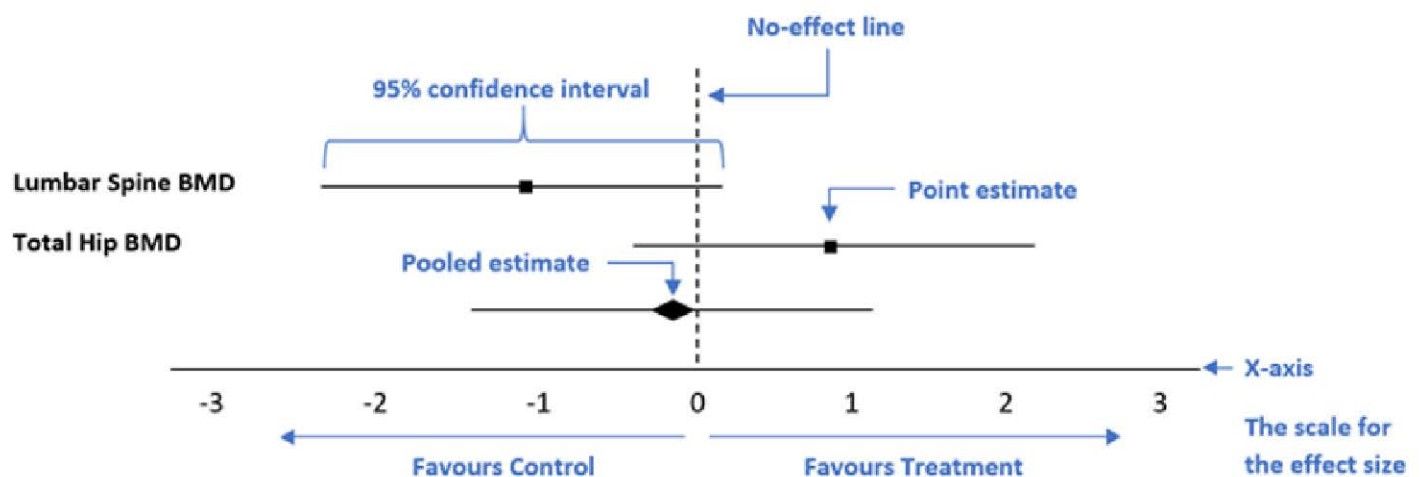
homogeneity of effect sizes across studies. The interpretation of the pooled or combined results is shown by the diamond symbol at the bottom of the graph, which is a combination of all individual studies weighted for the sample sizes. Interpretation is the same as the results from the individual studies, and the horizontal axis of the diamond represents the 95% CI. If the diamond crosses the line of no effect, the overall effect is insignificant; otherwise, the overall effect is deemed statistically significant.

Results

Overview

We identified 5,482 potentially relevant records through our searches and reviewed their titles and abstracts. We assessed 222 articles for eligibility at the full-text level and ultimately included 124 studies (16 studies measured multiple outcomes and appear in multiple sections) (Figure C). Most studies pertained to key questions that address interventions for prevention and treatment of low bone mass and osteoporosis in the SCI population. Figure D depicts the literature search results for systematic reviews. Table B displays the 11 identified systematic reviews on related topics that were used to inform section background information and narrative components of the discussion.

Figure B. Forest plot depicting standardized mean difference as a measure of effect. BMD, bone mineral density.



Excluded Studies

Ninety-eight full-text articles were excluded from this review. Reasons for exclusion included non-English language, animal studies, review articles that

were narrative or descriptive in nature, not enough individuals with SCI included, or a duration of the intervention or outcome evaluation of less than 6 months

Figure C. Literature search results for the key questions.

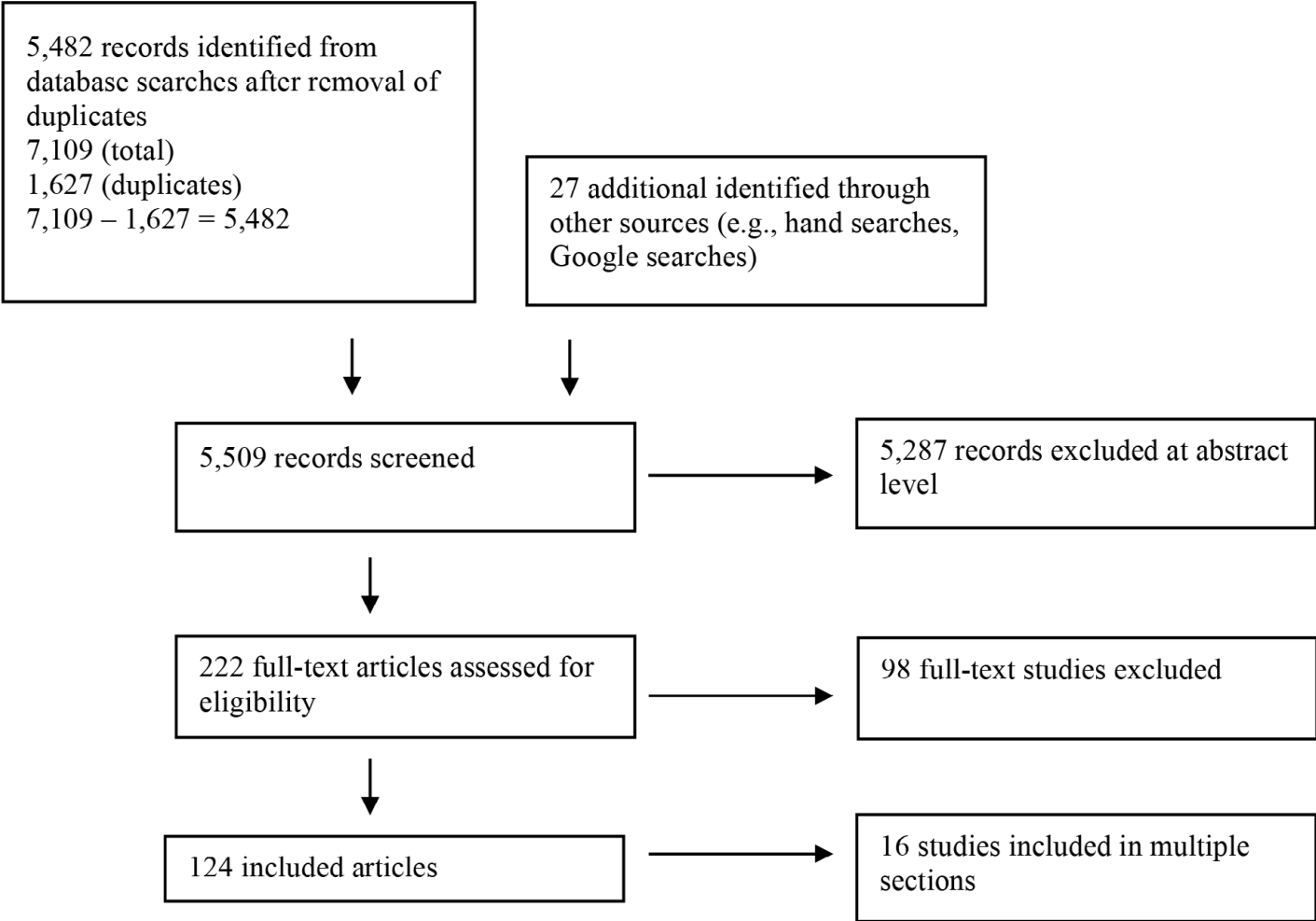


Figure D. Literature search results for systematic reviews.

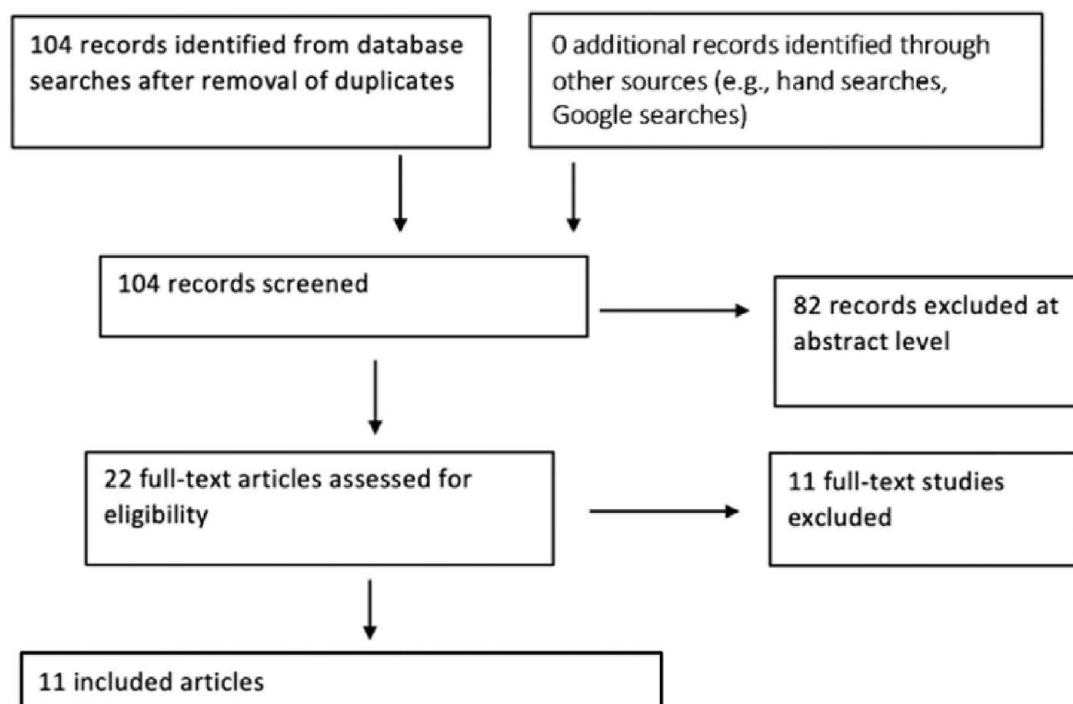


Table B. Summary of Literature Results of Systematic Review Search

Author	Year of Publication	PMID	Title
Ashe et al. ⁹	2007	22767990	Prevention and treatment of bone loss after a spinal cord injury: a systematic review
Biering-Sorenson et al. ¹⁰	2009	19172152	Non-pharmacological treatment and prevention of bone loss after spinal cord injury: a systematic review
Bryson & Gourlay ¹¹	2009	19810623	Bisphosphonate use in acute and chronic spinal cord injury: a systematic review
Chang et al. ¹²	2013	24278386	Effectiveness of bisphosphonate analogues and functional electrical stimulation on attenuating post-injury osteoporosis in spinal cord injury patients – a systematic review and meta-analysis
Charmetant et al. ¹³	2010	21094110	Diagnosis and treatment of osteoporosis in spinal cord injury patients: a literature review
Miller et al. ¹⁴	2016	27042146	Clinical effectiveness and safety of powered exoskeleton-assisted walking in patients with spinal cord injury: systematic review with meta-analysis
Paleg & Livingstone ¹⁵	2015	26576548	Systematic review and clinical recommendations for dosage of supported home-based standing programs for adults with stroke, spinal cord injury and other neurological conditions
Panisset et al. ¹⁶	2016	26345485	Does early exercise attenuate muscle atrophy or bone loss after spinal cord injury?

Author	Year of Publication	PMID	Title
Soleyman-Jahi et al. ¹⁷	2017	28497215	Evidence-based prevention and treatment of osteoporosis after spinal cord injury: a systematic review
van der Scheer et al. ¹⁸	2017	28733344	Effects of exercise on fitness and health of adults with spinal cord injury: a systematic review
Zleik et al. ¹⁹	2019	29745791	Prevention and management of osteoporosis and osteoporotic fractures in persons with a spinal cord injury or disorder: a systematic scoping review

Development of Recommendations for this Clinical Practice Guideline

The panel presented and discussed draft recommendations at an in-person meeting in January 2020. We revised the recommendations to reflect the comments of panel members, and the revised versions were disseminated electronically to the group for additional comments, review, and discussion until final recommendations were approved.

Grading of Recommendations: Quality of Evidence and Strength of Panel Opinion

The GRADE approach is a system for rating the quality of a body of evidence in systematic reviews and other evidence syntheses, such as health technology assessments and health care guidelines. It provides a framework for specifying health care questions, choosing outcomes of interest and rating their importance, evaluating the available evidence, and bringing together the evidence with considerations of values and preferences of patients and society to arrive at recommendations. Furthermore, the system provides clinicians and patients with a guide to using those recommendations and clinical practice and policy makers with a guide to their use in health policy.

The panel assigned a grade for each recommendation based on the American College of Chest Physicians modification of the GRADE system.^{20,21} The recommendation grade includes both the quality of

the evidence informing the recommendation and the panel's strength of opinion that the recommendation should (or should not) be considered in the care of individuals with SCI. In general, systematic reviews of RCTs represent the strongest-quality evidence, followed by individual RCTs, observational cohort studies, case series, and expert opinion. Factors that can modify the quality of evidence include risk of study biases; the precision, consistency, and directness of the results; and effect size.

The 3-tiered quality assignment (A, B, C) used is similar to that used by the American Association of Neurological Surgeons/Congress of Neurological Surgeons in the development of guidelines for the management of patients with cervical SCIs.^{22,23}

The **quality of evidence** is described by numerals: 1 (high), 2 (moderate), 3 (low), or 4 (very low). The **strength of evidence** is described by letters: A (strong), B (moderate), C (weak), or D (very weak).

Each recommendation includes both the **numerical** strength of the quality-of-evidence grade and the letter panel assessment of the strength of the recommendations. Table C describes the quality/strength of evidence and the designation and wording stipulations.

Table C. Grading of Quality and Strength of Evidence

	Benefits vs. Risk and Burdens	Methodological Strength of Evidence	Implications for Practice: Wording of Recommendation
1A = strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burden or vice versa	Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies	Recommendation can apply to most patients in most circumstances. “We recommend . . .”
1B = strong recommendation, moderate-quality evidence	Benefits clearly outweigh risk and burden or vice versa	Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise) or very strong evidence from observational studies	Recommendation can apply to most patients in most circumstances. “We recommend . . .”
1C = strong recommendation, low-quality evidence	Benefits clearly outweigh risk and burden or vice versa	Evidence for at least 1 critical outcome from observational studies, case series, RCTs with serious flaws, or indirect evidence	Recommendation can apply to most patients in many circumstances. “We recommend . . .”
1D = strong recommendation, very low-quality evidence	Benefits clearly outweigh risk and burden or vice versa	Evidence has significant flaws. Expert opinion includes evidence in the context of experts’ experiences and knowledge or experts’ interpretation of uncontrolled case series (e.g., in own practice)	Recommendation can apply to most patients in many circumstances. “We recommend . . .”
2A = weak recommendation, high-quality evidence	Benefits closely balanced with risks and burden	Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies	The best action may differ depending on patient circumstances or societal values. “We suggest . . .”
2B = weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burden	Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise) or very strong evidence from observational studies	The best action may differ depending on patient circumstances or societal values. “We suggest . . .”
2C = weak recommendation, low-quality evidence	Uncertainty in the estimates of benefits, risk, or burden	Evidence for at least 1 critical outcome from observational studies, case series, or RCTs with serious flaws or indirect evidence	Other alternatives may be equally reasonable. “We suggest . . .”
2D = weak recommendation, very low-quality evidence	Very little confidence in estimates of benefits, risk, or burden	Lack of evidence for at least 1 critical outcome from observational studies, case series, or RCTs with serious flaws or indirect evidence	Other alternatives are not able to be assessed. “One may . . .”

Consensus Recommendations

Consensus processes were used to arrive at the wording for contentious recommendations. Majority votes supported 65 of the 69 initial recommendations. The majority of recommendations had 80% or more support from the panel: 9 had between 80% and 91% support, and 56 had 100% support.

Four recommendations of the initial 69 required extensive discussion, after which draft recommendations were circulated to the panel

members for independent electronic voting. After electronic voting, 1 recommendation received 100% support, 1 received 91% support, and 2 received 70% support.

Following peer review by 35 members of partner organizations within the Consortium, 3 new recommendations were developed, 22 recommendations underwent wording revisions for clarity, 5 recommendations without sufficient evidence were removed, and 22 clinical considerations

were revised for further clarity. A revote was held on additions and revisions to the recommendations based on reviewer feedback, resulting in the presentation of 64 recommendations in the final CPG.

The preface **“we recommend”** infers strong evidence and that the recommendation can apply to most patients in most circumstances.

The preface **“we suggest”** infers moderate evidence and that the best action may differ depending on patient circumstances or societal values.

The preface **“one may consider”** infers weak evidence, expert opinion, and/or that other alternatives could not be assessed.

Clinical Considerations

The panel members have tried to highlight important details and clinical provisos under the heading “Clinical Considerations” specific to each recommendation as it appears in the guideline.

As an example:

- 2.2 We recommend that premenopausal adult women with SCI and amenorrhea have laboratory measurements of prolactin, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol levels.

Clinical Consideration

2.2

Women with a history of persistent amenorrhea should be referred for further evaluation to the appropriate specialist (e.g., endocrinologist and/or gynecologist).

Exceptions to the Guideline Methodology

Section 3.0 of the guideline contains recommendations that are a direct excerpt from the International Society of Clinical Densitometry (ISCD) position statements for bone density testing among individuals with SCI.²⁴ These recommendations were based on a separate rigorous systematic review, whose methodology, and the entire consensus opinion of ISCD panel members,^{24,25} are shown in Appendix D. ISCD recommends routine DXA measures of the distal femur and proximal tibia where population-specific normative data are available.²⁶ Section 8.0 of the guideline comprises a narrative review with expert consultation and panel consensus used to inform the recommendations. The recommendations in Section 8.0 pertaining to venous thromboembolism prophylaxis were derived through consultation with Dr. W. H. Geerts, an international thrombosis expert who acted as a consultant to the panel. The venous thromboembolism prevention and treatment recommendations were endorsed by the panel and the Orthopaedic Trauma Association (OTA) Delphi Consensus Panel led by William T. Obrebsky and Laura Carbone.²⁷ The recommendations in Section 8.0 pertaining to rehabilitation post-fracture healing represent the consensus opinions of occupational and physical therapists collaborating with the OTA task force and panel member expertise.²⁸

Recommendations and Rationales

1.0 MEDICAL HISTORY, ASSESSMENT OF FRACTURE AND FALL RISK

Preamble

It is vital for both the treating clinician and the individual with spinal cord injury/disease (SCI/D) to identify and understand their modifiable and non-modifiable risk factors for fragility fracture. This section addresses the importance of taking a detailed medical history and reviewing clinical or non-bone mineral density (BMD) risk factors for lower extremity fracture, including falls among adults with SCI/D. These assessments will inform clinical decision making regarding diagnostic tests such as laboratory screening (see Section 2.0) or bone density testing (see Section 3.0) in order to provide a preliminary assessment of fracture risk and to discern the need for fall prevention interventions. A succinct summary of key components of a bone health-related physical examination are provided.

Medical History

Key components of the medical history include inquiry about family history of osteoporosis, parental hip or wrist fracture, prior fragility fractures and BMD testing, history of falls, and functional abilities, including ambulatory status and use of assistive devices for transfers and mobility. In addition, a detailed review should be undertaken of the individual's prior or current medical conditions such as hyperthyroidism, hyperparathyroidism, Cushing's disease, and hypogonadism. Malabsorption syndromes such as sprue should be specifically sought with questions regarding unexplained diarrhea, steatorrhea, and weight loss, as these syndromes may have been relatively occult and not previously diagnosed. In women, menstrual history is important, including date of menarche, regularity of menses, and, if applicable, date of menopause. History and length of amenorrhea should be sought that may have been a consequence of an eating disorder, polycystic ovarian syndrome, or the spinal injury itself. In men, a history of hypogonadism or symptoms of low testosterone or alcoholism should be sought. Inquiry regarding changes in standing height, seated height, or iliacostal distance may identify an interval compression fracture. Clinicians may find

that questions regarding the individual's history, or signs and symptoms of the conditions listed in Table 1.1, helpful in organizing their inquiry.

Table 1.1. Secondary Causes of Low BMD Unrelated to SCI

Yes	No	Category	Medical history
		Inherited	Osteogenesis imperfecta
			Homocysteinemia
			Marfan's syndrome
		Nutritional	Malabsorption – Crohn's or colitis
			Chronic liver disease
			Alcoholism
			Calcium deficiency
			Vitamin D deficiency
		Endocrine	Hypogonadism (men and women)
			Hyperthyroidism
			Hyperparathyroidism
			Anorexia nervosa
			Hypercalciuria or kidney stones
		Other	Renal failure
			Multiple myeloma
			Rheumatoid arthritis
			Anorexia
			Mastocytosis
			Prostate cancer
			Breast cancer
			Prior chemotherapy or radiotherapy

Adapted from Lewiecki EM. Osteoporosis: clinical evaluation [updated 2021 Jun 7]. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK279049/>

Medication History

A number of medications are associated with increased fracture risk²⁹; thus, a detailed medication history is critical. Among these medications, use of opioids and anticonvulsants may be of particular concern, as these are commonly taken by individuals with spinal cord injury (SCI) and are associated with fracture

risk.³⁰ In addition, ascertainment of prior treatments for osteoporosis; use of calcium and vitamin D supplements; dietary intake of calcium (see Section 5.0); and review of tobacco, cannabinoid,³¹ and alcohol use are appropriate.

A detailed review of modifiable and non-modifiable risk factors for fracture should be completed prior to conducting an osteoporosis-specific physical examination.

Risk Factors for Fractures

Recommendations

- 1.1 We recommend that clinicians routinely assess fracture risk at least on an annual basis.
1B
- 1.2 We recommend that clinicians assess non-bone mineral density (BMD) risk factors for fracture following a change in functional abilities, minor injury after a fall, or a fragility fracture (see risk factor checklist in Table 1.2).
1B
- 1.3 We recommend that clinicians use hip, distal femur, and proximal tibia region BMD and prior history of fracture as the primary considerations for predicting lower extremity regional fracture risk.
1B

Rationale

Fractures after SCI

Fractures related to non-traumatic events are referred to as “fragility fractures” (also known as osteoporotic fractures or low-impact fractures) and are common in chronic SCI. Fragility fractures have been defined in SCI as those that occur after a fall from standing or seated height or less, or in the absence of trauma such as during routine activities of daily living.³²⁻³⁵ Reports suggest that 20%-46% of individuals with SCI will experience a fracture during their lifetime.^{36,37} Frotzler and colleagues³⁸ recently reported fracture rates per 100 patient-years of 3.17 in women with SCI and 2.66 in men with SCI, vs. 0.85 in women without SCI and 0.21 in men without SCI. The majority of fragility fractures after SCI occur in the distal femur and proximal tibia regions.^{36,38-40} The most frequently reported mechanisms of fracture in the SCI population include transfers^{38,40} or falls.³⁹⁻⁴¹

Non-BMD Fracture Risk Factors

This section describes established non-BMD or clinical risk factors for fracture and loss of bone density. For the purposes of this discussion, “incident fractures” are those that occur after the initiation of testing or observation. “Prevalent fractures” are those that occurred in the past, prior to initiation of testing or observation. We found 7 articles that addressed non-BMD risk factors for incident fracture^{40,42-47} in chronic SCI and 6 articles that addressed risk for prevalent fracture based on non-BMD risk factors in chronic SCI⁴⁸⁻⁵³ (Appendix F).

In a series of related retrospective cohort studies of males with traumatic SCI,⁴⁴⁻⁴⁶ incident fracture risk increased with anticonvulsant use (hazard ratio [HR] 1.16; 1.20 with anticonvulsant polytherapy), heparin use (HR 1.28), and opioid use (HR 1.78). Shorter duration (<6 months of use) and higher doses of opioids were associated with increased fracture risk. Longer duration of injury and complete SCI were also identified as incident fracture risk factors, but data were not provided for these variables.⁴⁵ Black race (HR 0.78), incomplete SCI (HR 0.57), thiazide use (HR 0.74), and combination therapy with thiazide diuretics and vitamin D supplementation (HR 0.43) were associated with reduced risk of incident fracture.⁴⁶ Reports conflict regarding incident lower extremity fracture risk in tetraplegia compared with paraplegia, with 1 report suggesting reduced fracture risk (HR 0.79) in tetraplegia⁴⁴ and a second report of the same cohort suggesting increased fracture risk (HR 1.27).⁴⁶ The one difference in these cohorts was that persons taking osteoporosis medications were excluded from the second analysis.⁴⁶ Notably, the authors later confirmed in a larger cohort of veterans with over 3,000 incident fractures that paraplegia is associated with a higher risk of lower extremity fracture compared with that for tetraplegia (HR 1.23).⁴³

When considering male and female individuals with SCI 2 years or more after injury who are not taking osteoporosis medication, the following were also identified as incident fracture risk factors: traumatic SCI (HR 1.16), motor complete SCI (HR 1.34), injury duration (HR 1.01), Charlson Comorbidity Index score (HR 1.12), history of hip fracture 1 year prior (HR 4.08), history of non-hip fracture prior year (HR 4.01), and women >50 years of age compared with older men

(HR 1.54).⁴³ Female gender alone or as an interaction with age or time after injury are risk factors for fractures.^{30,54-56} Heavy alcohol use (>5 servings per day) has been identified as a risk factor for hospitalizations for osteoporotic fractures in men with chronic SCI.⁴⁰ In terms of biomarkers of fracture risk, increased plasma C-terminal telopeptide of type I collagen (CTX) was associated with prevalent fractures in chronic SCI (p=0.021, 95% confidence interval 2.0-4769.6).⁴⁷ However, this finding was based on few incident fractures (n=5) and therefore future research is needed to confirm this association and to establish CTX as a biomarker of fracture risk.

Non-BMD risk factors for prevalent fracture in chronic SCI include motor complete injury (odds ratio 1.7),^{48,49,51} family history of fracture (HR 1.5),⁵² lumbar injury (HR 1.9),⁵² and longer duration of injury.^{50,53} Crude fracture rates in chronic SCI were 2% in 1 study, double the fracture rates in uninjured controls (1%).⁵² In a retrospective chart review, fractures were observed 6.4 ± 2.4 years after SCI (range 2-10 years) and were observed only in men.⁴⁸ Similarly, injury duration was significantly greater in participants with a history of prevalent fracture than in those with no fractures (15.7 vs. 9.3 years).⁵³

We found 2932-34,⁵⁷⁻⁸² studies that reported risk factors for bone loss in acute and chronic SCI but that did not include incident or prevalent fracture as outcomes (Appendix D). Three of these articles^{64,70,78} reported factors associated with greater bone loss in acute SCI, including injury duration,^{70,78} complete injury,^{70,78} increased spasticity,⁷⁰ and decreased physical activity.⁷⁰ Bone loss at the hip of 12% was reported in the first 12 months after injury.⁷⁰ A longitudinal study of bone parameters by peripheral quantitative computed tomography reported a 15% reduction in trabecular BMD and a 7% reduction in cortical bone density at the tibia at 12 months after injury. This study found no association between spasticity or physical activity and degree of bone loss during this period.⁶⁴ Twenty-four publications assessed risk factors for bone loss in chronic SCI in both longitudinal and cross-sectional study designs.^{32,57-63,65-69,71-77,79-82} Many reported increased bone loss with longer injury duration.^{32,60-63,66-69,71,74-77,79,80} Osteoporosis prevalence was higher in individuals >5 years after

injury than in those <5 years after injury (48.2% vs. 16.7%, respectively),³² with the risk of osteoporosis greatest >5 years after injury (HR 3.56).⁶⁸ Similarly, BMD was lowest at 19 years after injury⁷⁹ in 1 study, and another reported bone loss at the knee and hip into the second decade after injury.⁵⁹ Complete SCI is also associated with risk of bone loss.^{61,65,66} Individuals with complete SCI were reportedly 617% more likely to have osteoporosis than were those with incomplete injuries.⁶⁵ Additional risk factors for bone loss include wheelchair use,^{33,34,73} smoking,^{53,63} age,^{65,66} tetraplegia,^{57,65,81} duration of bed rest after initial injury,⁶⁰ period of immobilization after surgery,⁷⁶ and time to resume physical activity after injury.^{58,72} Ambulation,^{33,34,68,73} electrical stimulation,⁶⁸ body mass index,^{34,65,68} spasticity,^{61,63} lipophilic statin use,³⁴ lean mass,⁷² basal metabolic rate,⁸² and duration of physical activity after injury are associated with reduced bone loss or increased bone density.⁷²

On the basis of these findings, injury duration is the most studied factor associated with prevalent fracture, incident fracture, and loss of bone density among individuals with SCI and is consistent with reports of fractures occurring 6-15 years after injury. Motor complete injury and wheelchair use are associated with a risk of declining bone mass and/or osteoporosis development, but limited information is available on fracture risk. Medications, including opioids and anticonvulsants, may be associated with fracture risk, but additional information is needed to clarify the impact of these drugs on bone health after SCI. Similarly, electrical stimulation, early mobilization, and early introduction of physical activity after SCI may mitigate bone loss, but additional work is needed to better quantify the exercise dose required to obtain an osteogenic effect. Reviewing an individual's fracture risk profile may identify modifiable non-BMD risk factors for fracture that may be addressed with targeted interventions (i.e., weaning off drug therapy, starting intake of supplements). Decisions regarding whether to consider the role of nutraceuticals, exercise, or drug therapy should be based on assessment of global fracture risk as measured by BMD values (see Section 3.0) and the global fracture risk profile.

Table 1.2. Fracture Risk Factor Checklist Prior to BMD Testing

Established Fracture Risk Factors	
	Osteogenesis imperfecta
	Alcohol intake > 5 servings per day ³⁹
	Paraplegia ^{42,43}
	Duration of SCI ≥ 10 years ⁴⁴
	Motor complete injury (AIS A-B) ^{42,44}
	Family history of fracture ⁵¹
	Hip fracture in the last year or prior lower extremity fracture
	Routine use of benzodiazepines, anticonvulsants (i.e., carbamazepine, phenytoin), heparin, opioid analgesia (≥28 mg morphine for a 3-month period) ⁴³⁻⁴⁵

Fall Risk Assessment

Recommendations

- 1.4 We recommend that clinicians routinely assess an individual's fall risk.
1A
- 1.5 We recommend following an injurious fall, that clinicians offer individuals with SCI fall prevention education, transfer/wheelchair skills upgrading, and/or balance training to reduce the risk of falls and increase their confidence in community participation.
1D
- 1.6 We suggest that, after a fall, clinicians reassess the individual's level of confidence in navigating their home and community environments with a view to mitigate future fall risk and/or fragility fracture.
2C
- 1.7 SCI rehabilitation programs may consider establishing SCI-specific fall prevention programs accessible to individuals with SCI across the continuum of care.
2D

Clinical Consideration

1.7

Education regarding (1) fall prevention strategies, (2) techniques to reduce injury when a fall occurs, (3) psychological and physical fall recovery practices, (4) peer-to-peer education, and (5) inclusion of SCI caregivers are key elements for fall prevention programs to support optimal community participation.

Rationale

Falls are a common occurrence in both hospital and community settings and frequently result in fragility fractures after SCI. Falls in the rehabilitation hospital setting can result in a wide range of consequences, including liability, increased patient length of stay, injuries, delayed rehabilitation, and greater care costs. Hospital falls are a safety concern and are typically tracked and reported as hospital harm data.⁸³ In rehabilitation care settings in particular, administrators agree that rehabilitation itself may present an inherent risk of falls as individuals with SCI work toward improving mobility and autonomy and preparing for community reintegration.⁸³ Determining a balance between the risk of injurious fall that may result in fracture and the educational benefits of controlled falls during therapy remains a challenge within the tertiary SCI rehabilitation care setting.⁸³

When community-dwelling individuals with SCI leave the rehabilitation care setting, falls remain a significant risk factor for fracture. Over half (54%-55%) of ambulatory individuals have experienced at least 1 fall at 6 months after discharge.^{84,85} Similarly, 40%-76% of individuals with chronic SCI report experiencing a fall within the last year,⁸⁶⁻⁸⁸ and 32%-51% report experiencing recurrent falls.^{87,89,90} The odds of experiencing a fall and recurrent falls may be higher among individuals who report higher fear of falling,^{86,90} who report a greater number of comorbid conditions,^{86,88} or who have a history of falls.⁸⁹⁻⁹¹ Individuals who spend a greater percentage of their time ambulating may also have an increased risk of falling.^{85,87,92} A series of large prospective observational studies have examined increased exercise frequency as a predictor of experiencing a fall, with conflicting

evidence.⁸⁶⁻⁸⁸ In addition, higher self-reported quality of life may reduce the odds of falling and experiencing a fall-related injury.^{87,89}

Although falls are a risk factor for fracture for all individuals with SCI, ambulatory individuals and wheelchair users experience different fall mechanisms and fall risk factors. Among ambulatory individuals with SCI, a 74%-75% fall risk has been reported.^{93,94} Individuals with incomplete SCI perceive their decreased muscular strength, environmental hazards, and loss of balance as the most common reasons for their falls.^{85,93,94} For those with incomplete injuries, walking without a walking aid significantly increased the risk of falling,⁹⁵ and additional findings showed that the use of a walker as a mobility aid reduced the odds of experiencing a fall.⁸⁶

In wheelchair users, up to 14%-34% of individuals experienced an injurious fall,^{89,96} and falls were most commonly reported while transferring or while maneuvering over uneven terrain.^{89,97} Nelson and colleagues⁹⁸ reported that pain in the previous 2 months, greater motor function, history of a fall, and inaccessible home entrance explained 81% of the variance for injurious falls. Other intrinsic factors, such as the presence of muscle spasms or weakness, and being distracted, may also increase risk of falls.⁹⁷ Timing of fall occurrence also differs, depending on an individual's mobility level. Singh and colleagues⁹⁹ determined that more ambulators reported falls during the daytime (73%) when compared with wheelchair users (50%; $p=0.022$), with most falls occurring within the home environment (63%); these findings are supported by a study by Brotherton and colleagues.⁸⁶

Falls pose a significant risk of injury, including fracture, and can have significant psychosocial complications. Of those who fall, 10%-41% self-report an injury,^{89,90,92} the majority of which are minor, including bruises, scrapes, and muscle/ligament strain or sprain. Fractures have been reported after 18% of falls in wheelchair users.⁹⁶ The psychosocial well-being of individuals with SCI may also be affected; the experience of a fall may lead to altered self-image,¹⁰⁰ concerns of falling,¹⁰¹ and avoidance or limitations in performing daily activities.¹⁰¹

The frequency of falls experienced early during community reintegration, and across the lifespan, highlights the importance of ongoing conversations regarding falls and risk of falls to reduce fracture occurrence. Balance training and fall perturbation therapy may be key elements of successful fall prevention programming for individuals with motor incomplete SCI with sufficient lower extremity function to initiate stepping.¹⁰² Recommendations concerning wheelchair modifications or behavioral strategies to reduce fall risk from a wheelchair user's perspective have been outlined by Singh et al.¹⁰³ Increasing the diameter of casters, increasing wheelchair seat dump, use of seatbelts or chest straps, and taking time when performing physical tasks (e.g., transfers) are among these recommendations,¹⁰³ considered part of a comprehensive, individualized, SCI-specific fall prevention plan. Kirby¹⁰⁴ advocates for advanced wheelchair skills to reduce the risk of accidents caused by tips and falls, outdoors or on ramps, observed by manual wheelchair users. Because of the various physical and psychological complications that individuals with SCI may face following a fracture, it is essential that risk factors be assessed throughout the individual's lifetime in both rehabilitation and community care settings.

Physical Examination Pearls

The physical examination should include examination of the sclera to exclude rare conditions such as osteogenesis imperfecta, palpation of the thyroid gland, examination of the spine for kyphosis or scoliosis, and neurological examination to describe neurological impairment. An assessment of the iliocostal distance and ear-to-wall distance are important for longitudinal monitoring. If the patient is ambulatory, a gait examination should be done. Examination of the joints and long bones is important to ascertain whether there are any occult fractures, contractures, or residual fracture deformity. In men, examination for testicular atrophy is important, and in women, evaluation for hirsutism should be done.

Upon completion of a detailed history and physical examination, clinicians should conduct appropriate laboratory screening and offer bone density testing to those with moderate-to-high risk of fracture.

2.0 LABORATORY SCREENING

Preamble

This section specifies appropriate laboratory screening for secondary causes of osteoporosis in the assessment of all adults with spinal cord injury (SCI). In addition, testing that is unique to each sex and special tests are discussed.

Context

Consideration for causes of osteoporosis other than the SCI itself, such as senile or postmenopausal-related bone loss, is important, as appropriate diagnostic workups may identify secondary causes of osteoporosis, which require additional management approaches. A directed medical history and physical examination is important to guide laboratory screening decisions.

This guideline discusses the laboratory workups to consider, after a medical history and physical examination have been done, when screening to evaluate skeletal health in individuals with SCI (sublesional osteoporosis [SLOP]), i.e., bone loss occurring below the level of injury.

Laboratory workups for secondary causes of osteoporosis are directed toward identification of underlying conditions that may increase fracture risk. In the able-bodied population, a number of professional societies have published guidelines relative to such laboratory workups/testing and include laboratory studies that are recommended for all individuals and laboratory testing that applies only to specific clinical scenarios.¹⁰⁵⁻¹¹¹

SCREENING FOR BONE HEALTH

Recommendations

- 2.1 We recommend that, in the context of bone health screening, all adult women and men with spinal cord injury (SCI), regardless of injury duration, should have measurements of serum 25-hydroxyvitamin D (25-(OH)D) done by a validated assay method; complete blood cell count; ionized calcium (or calcium adjusted for albumin), phosphate, intact parathyroid hormone, creatinine (and estimated glomerular filtration rate), bone-specific alkaline phosphatase and transaminases, hemoglobin A1C, and thyroid-stimulating hormone levels;

and 24-hour urine collection for calcium and creatinine excretion.

1C

Clinical Consideration

2.1

These laboratory measurements should be done as soon as possible after the patient establishes ongoing care with their physician, or if there is significant loss of bone mineral density, an incident fracture, or a change in a medical condition or medication that might be expected to influence osteoporosis risk.

Referral to an endocrinologist or appropriate subspecialist should be considered if there are unexplained serum or urine calcium levels (hyper or hypo) and/or if the workup is suggestive of hyperthyroidism or hyperparathyroidism. Referral to a nephrologist should be considered in those with chronic kidney disease stage 4 (CKD 4) (glomerular filtration rate [GFR] 15-29 mL/min) and CKD 5 (GFR 15 mL/min or less) or unexplained renal impairment.

Rationale

Vitamin D Deficiency and Insufficiency (Not Enough Vitamin D)

25-Hydroxyvitamin D (25-(OH)D) levels (i.e., the sum of vitamin D₂ and vitamin D₃) are among the most common laboratory tests ordered in the evaluation of secondary causes of SLOP in individuals who receive prescription therapies for osteoporosis. Approximately half of those tested have low levels of 25-(OH)D.¹¹² Risk factors for vitamin D deficiency include inadequate sunlight exposure, low dietary intake of vitamin D-containing foods, malabsorption syndromes, older age, and obesity. In addition, African Americans with SCI are at higher risk than Caucasians for vitamin D deficiency because melanin blocks absorption of UVB from sunlight. However, there are no reports that low levels of vitamin D are directly related to incident fractures in individuals with SCI.

It is critically important that 25-(OH)D levels be measured correctly.^{113,114} Liquid chromatography tandem mass spectrometry is currently considered to be the most accurate and precise method for measuring 25-(OH)D and vitamin D metabolites.¹¹⁵

A number of controversies remain regarding the optimal serum levels of 25-(OH)D for skeletal health.¹¹⁶ In the able-bodied population, the Institute of Medicine suggests that persons are at risk for absolute vitamin D deficiency relative to bone health with serum 25-(OH)D levels below 30 nmol/L (12 ng/mL), with some, but not all, at risk for inadequacy at levels between 30 and 50 nmol/L (12 and 20 ng/mL).¹¹⁷ In contrast, the Endocrine Society considers serum levels of 25-(OH)D between 75 and 125 nM (30-50 ng/mL) to be normal.¹¹⁸ Hummel et al.¹¹⁹ suggested that, in individuals with SCI, the threshold of 25-(OH)D for suppression of intact parathyroid hormone is approximately 94 nmol/L (37.6 ng/mL) and that secondary hyperparathyroidism is associated with elevated bone resorption. Thus, higher levels of 25(OH)D may be optimal for skeletal health in individuals with SCI compared with the levels in the able-bodied population.¹¹⁹ In support of this concept,¹¹⁹ others have suggested that secondary hyperparathyroidism with vitamin D deficiency may contribute to the development SLOP,^{120,121} although there is no consensus at the present time on levels of 25-(OH)D that would be most beneficial for fracture prevention in SCI. Setting the lower limit of 25-(OH)D at 75 nmol/L (30 ng/mL) was thought to be reasonable by authors of the International Spinal Cord Injury Endocrine and Metabolic Extended Data Set.¹²² To date, most studies in SCI use 50 nmol/L (20 ng/mL) as the threshold to define vitamin D deficiency and 75 nmol/L (30 ng/mL) to define suboptimal or insufficient vitamin D status.¹²³ Conservatively, using these cutoffs, at least 1 in 3 individuals with SCI has vitamin D deficiency.¹²¹

Hypercalcemia (High Serum Calcium Levels) and Hypocalcemia (Low Serum Calcium Levels)

The total serum calcium level in the blood is composed of free (ionized) calcium and calcium bound to anions, principally albumin. Serum albumin levels vary with illness and nutritional status; thus, measurement of ionized calcium levels in SCI is recommended.¹²² Measurement of a serum phosphate level in conjunction with the serum calcium level is important, as phosphate may be decreased in primary hyperparathyroidism and other metabolic bone disorders that can affect fracture risk, including rickets and oncogenic osteomalacia.¹²⁴ Hypercalcemia may occur acutely following SCI, particularly in the setting of immobilization in young males with complete injury who have dehydration.^{125,126}

However, other causes of hypercalcemia should be considered, including hyperparathyroidism, malignancy, vitamin D intoxication, granulomatous disease, and medication use (such as thiazide diuretics), among others.

If ionized calcium levels are low, consideration should be given to low calcium intake, vitamin D deficiency, malabsorption states, and hypoparathyroidism.

Hypercalciuria (High Urinary Calcium Levels)

Hypercalciuria has been defined as 24-hour urinary calcium excretion greater than 275 mg in men and greater than 250 mg in women (or 4 mg/kg/body weight/day), although this does not take into account urinary concentration, renal function, or weight.¹²⁷ Others have proposed that the upper normal limit of 24-hour urine calcium is 200 mg/day when consuming a constant diet restricted in calcium, sodium, and animal protein.¹²⁸

Young age, high levels of injury, and low-motor score are risk factors for immobilization-induced hypercalcemia after SCI.¹²⁹ The frequency of hypercalciuria is highest in the first 3 months after injury.¹²⁶ Hypercalciuria is associated with elevated bone resorption.¹³⁰ Calcium excretion may remain elevated for up to 1 year following injury and usually returns to normal by 18 months following injury.¹³¹ A new steady-state level between bone resorption and formation may be reestablished approximately 2 years after injury,¹³¹ although bone loss may continue during the chronic phases of immobilization.¹³² It is important for clinicians to obtain a dietary history of calcium, sodium, and protein intake; use of calcium and vitamin D supplements; medication history; and duration of SCI when interpreting 24-hour urine calcium results. High intakes of calcium, sodium, and protein and use of calcium supplements may increase calcium excretion. Medications such as loop diuretics may also increase calcium excretion, whereas thiazide diuretics¹³³ may decrease it. The relationship of vitamin D supplementation to hypercalciuria is controversial. Low levels of 25-(OH)D have been associated with renal stones.¹³⁴ Supplementation with vitamin D may cause hypercalciuria; however, this occurs in only a subset of individuals.¹³⁵⁻¹³⁸

Increased bone resorption following injury causes increased calcium excretion, which can lead to

nephrolithiasis¹³⁹ and osteoporosis.¹⁴⁰⁻¹⁴² Renal and bladder stone disease are a particular concern in SCI.¹⁴³ The U.S. National Spinal Cord Injury Statistical Center reported that the incidence of renal calculi after the first year of SCI was 8 in 1,000 person-years.¹⁴⁴ Longer term follow-up of patients with a traumatic SCI suggests that the cumulative proportion with renal calculi approaches 38% by 45 years.¹⁴⁵ The risk for recurrent renal and bladder calculi is substantial, with reported frequencies of between 35% and 64% within 5 years of injury.^{146,147} Calcium-containing stones occur at least in part from the elevated bone resorption and hypercalciuria following immobilization. Infectious stones from chronic urinary tract infections and bladder management techniques (e.g., catheterization) are also problematic,¹⁴⁸ although their frequency may be decreasing.

In addition to idiopathic hypercalciuria, first reported by Albright et al.,¹⁴⁹ causes of secondary hypercalciuria include primary hyperparathyroidism, hyperthyroidism, Paget's disease, multiple myeloma (MM), malignancy, sarcoidosis, renal tubular acidosis, and drug-induced urinary calcium losses. Immobilization-induced hypercalciuria may be of particular concern in individuals with SCI.¹⁵⁰ Vitamin D supplementation may increase urinary calcium excretion.¹⁵¹ A number of other factors, including body weight, calcium intake, intestinal absorption, estrogen status (women), and other micro and macronutrients are reported to influence calcium excretion.¹⁵²⁻¹⁶²

There are nonpharmacological and pharmacological therapies that can improve hypercalciuria. Lowering sodium intake may lower calcium excretion, although the effect is small, as urinary calcium rises by only 20-40 mg/day for every increase of 2,300 mg of sodium in the diet.^{156,157} Similarly, although lowering protein intake may decrease calcium excretion, the effect is small (about 1 mg/g protein).¹⁶³ Thiazide diuretics reduce calcium excretion, and in a report that included over 6,000 males with SCI (1,433 thiazide users and 5,536 nonusers), filled prescriptions for thiazide diuretics were associated with an approximately 25% risk reduction in incident lower extremity fractures.⁴⁶ However, no clinical trials have prospectively examined whether thiazides diuretics do indeed reduce fracture rates in individuals with a SCI.

Hypocalciuria (Low Urinary Calcium Levels)

Urinary calcium levels below 50-100 mg/24 h in able-bodied women and men on unrestricted diets are considered to be abnormal; Heaney et al. recommended that a lower limit of 40 mg/24 hours be used for women.¹⁶⁴ Hypocalciuria (after consideration for race, as multiple reports suggest that calcium excretion is lower in African Americans than in whites)¹⁶⁵⁻¹⁶⁷ or medications that can cause hypocalciuria (e.g., thiazide diuretics) should prompt further investigation for low calcium intakes, vitamin D deficiency, and malabsorption states (particularly celiac disease).

Treatment for hypocalciuria is tailored toward the problem identified (e.g., vitamin D supplementation if vitamin D deficiency is the cause identified, or a gluten-free diet if celiac disease is identified).

Anemia

Both iron deficiency and iron overload have been associated with osteoporosis in the able-bodied population.¹⁶⁸ In elderly postmenopausal women in the Women's Health Initiative, anemia was positively associated with incident fractures.¹⁶⁹ Although this association has not been reported in individuals with SCI, anemia is a prevalent condition in this population. Further, iron deficiency anemia may be a finding in celiac disease.¹⁷⁰

Kidney Disease

In the able-bodied population, individuals with chronic kidney disease (CKD) are reported to be at increased risk of fractures; this risk increases as renal disease progresses, such that the risk of fracture is 4 times higher in individuals with end-stage renal disease than it is in healthy controls.¹⁷¹ In individuals with SCI, renal function can deteriorate as part of aging and/or in relation to neurogenic bladder dysfunction and its complications. In a study of veterans, 1 in 3 had renal disease that was defined as an estimated glomerular filtration rate (GFR) of <60 mL/min/1.73 m, but the majority (over 80%) had CKD 1 (GFR > 90 mL/min) or CKD 2 (GFR 60-89 mL/min), less than 10% had CKD 3 (GFR 30-59 mL/min), and less than 5% had CKD 4 (GFR 15-29 mL/min) or CKD 5 (GFR 15 mL/min or less).¹⁷² Other forms of renal osteodystrophy, which may present as fractures or low bone mineral density (BMD), are more frequent in advanced renal disease.¹⁷³

Liver Disease

Whether hepatic disease is related to bone loss or fractures in the able-bodied population is controversial.^{174,175} In individuals with SCI, abnormalities in hepatic function are common. In 1 report that included 55 men with chronic SCI, almost half had nonalcoholic fatty liver disease, which was associated with low testosterone levels.¹⁷⁶ A retrospective study of 500 individuals with SCI in Korea who underwent screening with abdominal ultrasounds found that approximately 15% of patients had a fatty liver.¹⁷⁷

Diabetes Mellitus

Impaired glucose tolerance and type 2 mellitus are prevalent in patients with a SCI.¹⁷⁸⁻¹⁸⁰ Diabetes are frequently unrecognized.^{179,181} Clinical practice guidelines relative to cardiometabolic risk after SCI recommend that adults with SCI be screened for diabetes and prediabetes, with repeat testing at least every 3 years if test results are normal.¹⁸² However, there are no specific studies on the risks of osteoporosis or fracture in individuals with SCI who have impaired glucose tolerance, type 1 diabetes mellitus, or type 2 diabetes mellitus. In the able-bodied population, fracture risk, particularly for hip fractures, is substantially increased in both type 1 and type 2 diabetes.^{183,184} Thus, because of the prevalence and known impact of diabetes on skeletal health in the able-bodied population, an important consideration in individuals with SCI is an assessment for impaired glucose tolerance and diabetes mellitus as part of the screening laboratory evaluation for secondary causes of osteoporosis.

Thyroid Disease

In the able-bodied population, hyperthyroidism and subclinical hyperthyroidism,¹⁸⁵ whether from endogenous causes such as Graves' disease¹⁸⁶ or from iatrogenic overreplacement with exogenous thyroid hormone,¹⁸⁷ are associated with increased fracture risk. In addition to these conditions, there may be unique considerations relative to thyroid disease in SCI. Acutely following SCI, serum levels of both T3 and T4 are decreased,¹⁸⁸ particularly in men and those with paraplegia.¹⁸⁹ Further, pituitary declines in thyroid-stimulating hormone (TSH) in individuals with chronic SCI may play a small role in the pathogenesis of SLOP itself.¹⁹⁰ Thus, assessment of thyroid function in the workup of secondary causes of SLOP is important.

However, in the spirit of choosing wisely, the American Society for Clinical Pathology recommends not ordering multiple tests when initially evaluating a patient who may have thyroid disease. It recommends starting with a TSH test, and if the result is abnormal, following up with additional tests.¹⁹¹

Several screening laboratory studies routinely done in clinical practice for general health reasons, including measurement of complete blood counts and renal, hepatic, and thyroid function, are routinely recommended in the laboratory workup for secondary causes of osteoporosis in the able-bodied population.^{174,192-196}

Sex Considerations

WOMEN

Recommendations

- 2.2 We recommend that premenopausal adult women with SCI have the laboratory tests listed in 2.1, with additional measurements of prolactin, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol levels.
- 1D

Clinical Consideration

2.2

Women with a history of persistent (defined as lasting more than 6 months after injury onset) oligomenorrhea or amenorrhea or abnormalities in prolactin, FSH, LH or estradiol should be referred to an endocrinologist for further evaluation.

Rationale

Premenopausal Women

Low bone mass (based on dual-energy X-ray absorptiometry measurements) in premenopausal able-bodied women may reflect small bone size, low peak bone mass, or bone loss and does not have the same clinical implications related to fracture risk as in postmenopausal women. Premenopausal able-bodied women with low BMD, and without other risk factors for fracture, have a low short-term fracture risk.¹⁹⁷ Initial laboratory workup for premenopausal women with low BMD is similar to that of postmenopausal women; additional studies that may be needed include

measurement of estradiol, LH, FSH, and prolactin levels and screening for celiac disease.¹⁹⁷

Menstrual history is an essential component of the workup of bone mass in premenopausal women. In the able-bodied population of premenopausal women with amenorrhea or oligomenorrhea, comprehensive laboratory workups to exclude functional hypothalamic amenorrhea should be considered.¹⁹⁸ Moreover, a careful assessment should be done for polycystic ovarian syndrome, as it is associated with low bone mass. It is characterized by chronic anovulation, clinical/biochemical parameters consistent with hyperandrogenism, and/or polycystic ovaries on imaging studies.¹⁹⁹ Insulin levels and the LH/FSH ratio are often elevated in this syndrome.²⁰⁰

In women with SCI, post-injury amenorrhea is common, with almost 50% experiencing at least transient disruption of the menstrual cycle following injury.²⁰¹ The majority of women resume their menstrual periods by 6 months following injury,^{202,203} although cases of longer periods of amenorrhea, with resumption of menses occurring up to 30 months after injury, have been reported.²⁰³

Postmenopausal Women

Menopause is defined as the absence of menses for 12 consecutive months with no other biological or physiological cause identified. Biochemically, in this setting, elevated FSH levels consistently at 30 IU/mL or higher are characteristic. In the able-bodied population, menopause is recognized as a period of rapid bone loss, particularly during the first 5 years. During the first year following menopause, annual rates of loss are approximately 1.8%-2.3% in the spine and 1.0%-1.4% in the hip; if this rate of bone loss continues for 5 years, on average, a women's areal BMD will decrease 7%-10% in the spine and 5%-7% in the hips.²⁰⁴

Increasingly recognized, however, is the importance of the perimenopausal period, particularly late perimenopause, for bone loss in women. The Study of Women's Health Across the Nation (SWAN) defined (by self-report) early perimenopause as women with menstrual bleeding in 1, 2, or 3 of the last 3 months who had also noted a change in bleeding pattern from their prior menstrual pattern, and late perimenopause

as bleeding in at least 1 of the last 11 months, but not in the last 3 months.²⁰⁴ In women of every ethnicity included in SWAN (non-Hispanic whites, Chinese, Japanese, Hispanic, black), late perimenopausal bone loss was rapid and essentially equivalent to that of postmenopausal bone loss. In contrast, early perimenopausal bone loss either did not occur or happened at clinically insignificant rates.²⁰⁵ FSH levels may identify perimenopausal women who are more likely (or not) to begin losing bone within 12 months, especially at the lumbar spine.²⁰⁶

The importance of recording menopausal status in women with SCI is recognized, and information on menopausal status is collected as part of the International Spinal Cord Injury Endocrine and Metabolic Function Basic Data Set.¹⁸¹

MEN

Recommendation

- 2.3 We recommend that adult men with SCI have the laboratory tests listed in 2.1, with additional measurements of LH, FSH, and morning fasting serum bioavailable testosterone levels.

1D

Clinical Consideration

2.3

Referral to an endocrinologist and/or urologist may be considered if testosterone, LH, or FSH levels are abnormal.

Rationale

In able-bodied men, the 3 most common secondary causes of osteoporosis are alcohol abuse, glucocorticoid excess (usually from chronic therapy), and hypogonadism.²⁰⁷

Hypogonadism (Low Serum Testosterone Levels)

Le et al.¹¹² reported that hypogonadism was the most frequent laboratory abnormality identified in a cohort of almost 200 individuals with SCI, who had filled prescriptions for Food and Drug Administration-approved osteoporosis medications, more half of them having low levels of testosterone.

In the able-bodied population, the Endocrine Society²⁰⁸ recommends measurements of free or bioavailable testosterone (with sex hormone-binding globulin [SHBG]) in the workup of secondary causes of osteoporosis in men. The Endocrine Society recommends that a serum total testosterone concentration of <300 ng/dL (equivalent to 10.4 nmol/L) should be considered low²⁰⁹; some studies in men with SCI have defined low levels of testosterone as a serum total testosterone concentration of <11.3 nmol/L (325 ng/dL).^{210,211} Serum testosterone levels exhibit diurnal variation and are highest in the morning; thus, it is recommended that blood samples be drawn early in the morning.²¹²

The Endocrine Society recommends establishing a diagnosis of hypogonadism only in men with symptoms and signs consistent with testosterone deficiency and unequivocally and consistently low serum testosterone levels. Biochemical confirmation of hypogonadism is based on 2 separate morning fasting total testosterone concentrations (or free testosterone in men whose total testosterone result is near the lower limit of normal or who have a condition that alters SHBG). Testing for free testosterone should be obtained by using equilibrium dialysis or estimated from total testosterone, SHBG, and albumin. Additional diagnostic evaluations to ascertain the cause of androgen deficiency (i.e., hypothalamic, pituitary, and/or testicular dysfunction) are recommended. In primary hypogonadism from testicular dysfunction, FSH and LH levels are elevated; in secondary hypogonadism, FSH and LH levels are low or low-normal.

Special Tests Recommendations

- 2.4 One may consider protein electrophoresis in individuals over 50 years of age or individuals who present with a vertebral compression fracture of unknown etiology.
2D

Clinical Consideration

2.4

Referral to a hematologist may be considered if there is laboratory evidence suggestive of monoclonal gammopathy.

- 2.5 One may consider the following additional testing if clinically indicated:
- 24-hour urinary cortisol/overnight dexamethasone suppression test if Cushing's disease is suspected
 - Anti-tissue transglutaminase immunoglobulin A antibody if celiac disease is suspected
- 2D

Clinical Consideration

2.5

Cushing's disease should be suspected if the physical examination shows striae (wide and purple; particularly over abdomen or axilla), weight gain, truncal obesity, weight gain on the posterior neck (buffalo hump), acne, facial plethora, hirsutism, and/or hypertension. Associated ancillary laboratory abnormalities may include an elevated blood glucose level.

Celiac disease should be suspected if there are symptoms of malabsorption (i.e., weight loss, diarrhea, bloating) and/or a rash consistent with dermatitis herpetiformis. Associated ancillary laboratory abnormalities may include iron deficiency anemia, hypovitaminosis D (low 25-(OH)D), and/or hypocalciuria. Referral to a gastroenterologist may be considered.

Rationale

Multiple Myeloma

In the able-bodied population with osteoporosis, testing for less common causes of osteoporosis is more often targeted to selected high-risk groups. For example, MM and its more common potential precursor monoclonal gammopathy of uncertain significance (MGUS) are recognized causes of secondary osteoporosis and fragility fractures in the elderly able-bodied population.^{213,214} In 1 report, over time, approximately 80% of all patients with MM experienced a pathological fracture.²¹⁵ The prevalence of MGUS in the able-bodied population over the age of 50 is approximately 3%-4% when serum protein electrophoresis is used as a screening test.²¹⁶ Thus, in the able-bodied population, some authors have suggested that it is reasonable to target and test only those over the age of 50 who have osteoporosis

or an osteoporotic-related fracture for MM.²¹⁷ Among individuals with SCI, 10%-15% of all patients who present with spinal cord compression from a malignancy have MM as the cause.²¹⁸

Cushing's Disease

Another infrequent secondary cause of osteoporosis in the able-bodied population is Cushing's disease.^{219,220} However, in the absence of other clinical clues that Cushing's is present, routine assessment for it is not usually part of the workup for osteoporosis. In support of this, the National Osteoporosis Guidelines Group²²¹ and the National Osteoporosis Foundation¹⁹⁵ have suggested that assessments of cortisol levels with 24-hour urinary free cortisol/overnight dexamethasone suppression testing and urinary free cortisol be performed only as clinically indicated.

The adrenal pituitary axis is dysregulated following SCI, and circulating levels of cortisol may increase acutely following injury.²²² However, there are no reports that Cushing's disease occurs more commonly in individuals with SCI than in the healthy able-bodied population. There is only 1 case report of an adrenocorticotrophic hormone-secreting pituitary carcinoma causing spinal cord compression.²²³ Thus, because Cushing's disease is uncommon and usually associated with other clinical symptoms and physical examination findings, Craven et al.¹⁹⁶ did not include routine screening for Cushing's disease in the absence of other clinical indications in the workup of SLOP in patients with chronic SCI.

Celiac Disease

Celiac disease (nontropical sprue) should be suspected if there are symptoms of malabsorption, including diarrhea, weight loss, and bloating, particularly in the setting of hypocalciuria, hypovitaminosis D, and iron deficiency anemia; hypocalcemia, with elevated intact parathyroid hormone and alkaline phosphatase levels, may also be present. The rash of dermatitis herpetiformis, a pruritic vesicular eruption usually present on the extensor surfaces of the elbows, knees, and buttocks, is a common extraintestinal manifestation of celiac disease.²²⁴ In the absence of immunoglobulin A (IgA) deficiency, laboratory screening for celiac disease is best done by the anti-tissue transglutaminase IgA antibody test.²²⁵

3.0 BONE DENSITY TESTING WITH DUAL-ENERGY X-RAY ABSORPTIOMETRY

Preamble

This section highlights the importance of measuring bone mineral density (BMD) via dual-energy X-ray absorptiometry (DXA) at the hip, distal femur, and proximal tibia early after spinal cord injury/disease (SCI/D) and at appropriate intervals throughout the individual's lifetime to (1) diagnose osteoporosis or low bone mass (osteopenia), (2) assess fracture risk, and (3) evaluate treatment effectiveness. The natural history of changes in BMD following SCI/D are summarized below. The importance of measuring hip, distal femur, and proximal tibia BMD **while adhering to the International Society for Clinical Densitometry (ISCD) Position Statements regarding routine BMD testing after SCI/D are underscored.** The ISCD Official Positions are intended to inform clinical care and guide the recognition and diagnosis of osteoporosis and recognition of an individual's fracture risk following SCI.²²⁶

Bone Density Testing

DXA is a low-cost, widely available "gold-standard clinical technology" to measure areal BMD in g/cm² of the lumbar spine, hip, and wrist regions.^{227,228} The radiation dose associated with DXA scanning is 0.1 Sv or about 1/10th to 1/30th of a chest X-ray.²²⁹ In the general population, low BMD values are associated with a higher likelihood of fragility fracture and a greater likelihood of the patient benefiting from medical therapy.^{230,231}

In all cases, DXA scans for individuals with SCI/D should be performed in a room with an adequate turning radius for a manual or power wheelchair and be equipped with a lift to transfer individuals with SCI/D onto the densitometer for scan acquisition. The DXA scanner assumes that the region of interest selected for analysis contains only calcified hard tissue and homogeneous soft tissues.²³² A polycarbonate positioning device is typically used to ensure optimal positioning for scan acquisition of the hip (total and femoral neck), distal femur, and proximal tibia and to prevent movement artifacts. In persons without SCI, DXA is a powerful predictor of fracture, with fracture risk doubling for each standard deviation below peak

bone mass.^{233,234} A recent review by Cirnigliaro et al.²³⁵ highlights many of the available techniques for distal femur and proximal tibia scan acquisition. A protocol is publicly available for using Hologic lumbar spine software to acquire and analyze DXA scans of the distal femur and proximal tibia, as well as a data set to calculate distal femur and proximal tibia T-scores and Z-scores.²⁶ Although DXA is able to predict global fracture risk, DXA measurements at the knee (distal femur or proximal tibia) are most predictive of fractures at that site, so-called site-specific fracture prediction.^{236,237}

The measured DXA values can be used to (1) diagnose osteoporosis or low bone mass (see Table 3.1), (2) estimate the associated fracture risk by using risk prediction tools (e.g., Canadian Fracture Risk Assessment [FRAX] and Canadian Association of Radiologists and Osteoporosis Canada [CAROC] and/or an SCI-specific fracture risk tool),²³⁸⁻²⁴¹ and (3) monitor treatment effectiveness.

The diagnosis of sublesional osteoporosis can be made on the basis of hip, distal femur, or proximal tibia BMD values, as shown in Table 3.1.

Table 3.1. Definition of Sublesional Osteoporosis – the definitions applied are determined by the individual’s biological sex, and their age.²⁴¹

Age Range	Definition ^a
Males ≥ 50 years of age or postmenopausal females	Hip (total or femoral neck), distal femur, or proximal tibia T-score ≤ -2.5
Males < 49 years of age or premenopausal females	Hip (total or femoral neck), distal femur, or proximal tibia Z-score < -2.0, with ≥ 3 risk factors for fracture
Males or females age 18-90	Prior long bone or vertebral fragility and no identifiable etiology of low bone mass other than SCI

^aThe definitions applied are determined by the individual’s biological sex and age.²⁴¹
T-score = the number of standard deviations above (+) or below (-) the mean peak density.²⁴²
Z-score = the number of standard deviations above (+) or below (-) the mean density for an individual of that age and sex.²⁴²
Adapted from Craven et al.²⁴¹

A Z-score of -2.0 is a rationale intervention threshold for premenopausal females and young males with low bone mass. Identification of those persons with SCI who are at highest risk for fracture is important to guide treatment strategies. Typically, lifestyle interventions are offered for those with low fracture risk (see Sections 5.0 and 6.0) and lifestyle interventions with drug therapy are offered to those with high fracture risk (see Section 7.0) or a recent fracture (see Section 8.0).

Follow-up BMD testing after the initial assessment is best done at the same place, with the same densitometer, and, ideally, by the same technologist. It is important for DXA facilities to conduct short-term precision studies and to report their precision and the least significant change in g/cm² to consulting physicians. Follow-up BMD testing is typically done when the expected change in BMD exceeds the least significant change of the densitometer (typically, 12-36 months later). The current recommendation of the ISCD is to determine intervals between BMD testing according to each patient’s clinical status: typically, 1 year after initiation or change of therapy is appropriate, with longer intervals once therapeutic effect is established.²⁵

Following DXA testing , the absolute femoral neck, proximal tibia, and distal femur BMD may be evaluated to determine whether it is above or below the fracture threshold (Table 3.1), or the absolute value can be used to calculate individual fracture risk (Lala 2014²³⁷; Table 3.2).

Table 3.2. Knee Region Bone Mineral Density (BMD) Values

Term	BMD values (g/cm ²) ^a	Definition
Fracture threshold	≤0.78g/cm ²	Knee region BMD values below which fractures occur
Fracture breakpoint	<0.49 g/cm ²	Knee region BMD values at which the majority of fractures occur

aBMD values below the fracture threshold infer increased (i.e., low-moderate) fracture risk and BMD values below the breakpoint infer high fracture risk.

Source: Garland et al. 2005.⁵³

Table 3.3. Knee Region Areal Bone Mineral Density (BMD) Values Can Be Used to Predict Knee Region Fracture Risk

DXA Scan Site (g/cm ²)	Fractures (Unadjusted) OR (95% CI) ^b	p-Value	Fractures (Adjusted) OR (95% CI) ^b	p-Value
Proximal tibia BMD	6.5 (2.5, 23.0)	<0.001	6.1 (2.1, 23.6)	0.003
Distal femur BMD	4.9 (2.0, 15.9)	0.002	4.9 (1.7, 17.5)	0.006
Total hip BMD	2.4 (1.3, 5.1)	0.009	1.9 (1.0, 4.1)	0.083
Femoral neck BMD	2.1 (1.2, 4.0)	0.019	1.7 (0.9, 3.4)	0.093
Proximal tibia BMD	6.5 (2.5, 23.0)	<0.001	6.1 (2.1, 23.6)	0.003

Data are from a prospective study of 70 individuals with chronic SCI²³⁷; 19 of 70 participants with 38 fractures: 3 hip, 16 femur, 11 tibia, and 5 ankle. OR per standard deviation decrease, adjusted for motor complete injury.

Source: Lala et al. 2014²³⁷

DXA measures of the hip, distal femur, or proximal tibia regions of interest containing technical artifacts, such as hardware, heterotopic ossification, contracture, or movement artifact secondary to spasticity, or leg bag artifacts, which prevent optimal positioning for scan acquisition or limit the accuracy of the analysis, should not be used for diagnosis, fracture risk assessment, or monitoring response to therapy.

Natural History of Changes in BMD

There are substantial rapid decreases in hip,²⁴⁴⁻²⁴⁷ distal femur,^{245,246} and proximal tibia BMD early after SCI among those with motor complete injury. The majority of individuals with SCI 2 or more years post-injury have osteoporosis or low bone mass.²⁴⁸⁻²⁵⁰ Among individuals with chronic SCI, BMD declines at the hip,²⁵¹⁻²⁵⁴ distal femur,²⁵⁵ and proximal tibia^{251,255} are ongoing for at least 5 years.²⁵⁵ There is some controversy regarding whether BMD stabilizes at a new lower threshold some years post-injury or continues to decline with aging.²⁵⁶ Cirnigliaro et al.²⁵⁷ have reported ongoing declines in BMD of the hip, distal femur, and proximal tibia regions in the second decade after injury.²⁵⁷

The rate and severity of hip, distal femur, and proximal tibia decline are not as predictable or as well described in individuals with motor incomplete SCI/D as they are in those with motor complete injury. Individuals with SCI typically have a much lower bone mass than their age-matched peers in the general population without SCI. In addition to the individual's impairment causing their SCI, the rates of BMD decline also vary with age at injury onset, race, sex, medication use, and the individual's mobility (walking vs. wheelchair).

Low bone mass and elevated fracture risk are not clinically problematic until a fragility fracture occurs. Fragility fractures of the hip, distal femur, and proximal tibia regions are associated with increased morbidity²⁵⁸ and mortality.²⁵⁹ It is important that clinicians take a proactive approach to help patients maintain bone mass and reduce the risk of future fracture-related morbidity and mortality.

International Society for Clinical Densitometry

The International Society for Clinical Densitometry (ISCD) is an international professional association

dedicated to “advancing high quality musculoskeletal health assessment in the service of superior patient care.”²⁶⁰ With more than 2,700 members from more than 25 countries,²⁶⁰ the ISCD is dedicated to the education and certification of regulated health care professionals. It routinely publishes official positions and statements on important topics related to the application of DXA in a clinical setting and across patient populations.

With permission from Christopher Shuhart, former ISCD President, the “Bone Mineral Density Testing in Spinal Cord Injury: 2019 ISCD Official Position” is enclosed in Appendix D. We encourage all readers to review these positions in detail; a brief summary of the position development process, the guiding questions, and formal ISCD Positions are found within this section. The Position Development Conference is intended to advance the field of skeletal assessment by developing position statements on important topics through a rigorous validated method.

This task force conducted a series of systematic reviews to guide the development of evidence-based position statements that were reviewed by an expert panel at the 2019 Position Development Conference in Kuala Lumpur, Malaysia. The Paralyzed Veterans of America (PVA) Bone Health and Osteoporosis Management Clinical Practice Guideline (CPG) panel acknowledges the real and perceived conflicts of interest, as 7 members were common to the ISCD Position Statement and PVA CPG panels.

The Position Development Conference was intended to answer 4 key questions:

1. What are the indications for initial DXA in individuals with spinal cord injury?
2. Can bone densitometry by DXA be used to diagnose osteoporosis, assess fracture risk, or monitor response to therapy in individuals with spinal cord injury?
3. How should DXA be used to monitor osteoporosis therapy (drug, nutraceuticals, rehabilitation interventions) in individuals with SCI?
4. Are there DXA based criteria that are absolute or relative contraindications to exercise-based therapy?

- 3.1 We recommend that clinicians adhere to the 2019 ISCD Adult Official Positions for DXA in Patients with Spinal Cord Injury.

1B

The entire ISCD Official Position Statements are in Appendix D. All clinicians are encouraged to read them.

Question 1: What are the indications for initial DXA in individuals with spinal cord injury?

ISCD Official Position #1

- 3.2 All adults with spinal cord injury resulting in permanent motor or sensory dysfunction should have a DXA scan of the total hip, proximal tibia, and distal femur as soon as medically stable.

1A

Question 2: Can bone densitometry by DXA be used to diagnose osteoporosis, assess fracture risk, or monitor response to therapy in individuals with spinal cord injury?

ISCD Official Position #2

- 3.3 In adults with SCI, total hip, distal femur and proximal tibia bone density should be used to diagnose osteoporosis, predict lower extremity fracture risk and monitor response to therapy where normative data are available.

1B

Question 3: How should DXA be used to monitor osteoporosis therapy (drug, nutraceuticals, rehabilitation interventions) in individuals with SCI?

ISCD Official Position #3

- 3.4 Serial DXA assessment of treatment effectiveness among individuals with SCI should include evaluation at the total hip, distal femur, and proximal tibia, following a minimum of 12 months of therapy at 1- to 2-yr intervals. Segmental analysis of total hip, distal femur and proximal tibia sub-regions from a whole-body scan should not be used for monitoring treatment.

1B

Question 4: Are there DXA based criteria that are absolute or relative contraindications to exercise-based therapy? (see Section 6.0 Rehabilitation Therapy)

ISCD Official Position #4

3.5 There is no established threshold BMD value below which weight-bearing activities are absolutely contraindicated. BMD and clinical risk factors should be used to assess fracture risk prior to engaging in weight-bearing activities.

1B

Clinical care has been previously limited by the lack of consensus-derived guidelines or standards regarding DXA-based diagnosis of osteoporosis, fracture risk prediction, or monitoring response to therapies. Although the bulk of evidence regarding bone health and SCI is derived from studies restricted to traumatic SCI, we recommend that the ISCD Position Statements be applied clinically to individuals with either traumatic or atraumatic SCI.

Successful implementation of the enclosed recommendations and ISCD Positions will require the SCI community to work collaboratively with health policymakers and payers to resolve feasibility dilemmas regarding bone density testing and the identification of patients with low bone mass or sublesional osteoporosis and high fracture risk who require therapy. Although DXA is the current clinical gold standard for assessment of bone density and fracture risk in North America, other technologies are used for research purposes or in Europe to assess volumetric BMD, bone strength, and bone architecture.

4.0 VOLUMETRIC BONE DENSITY AND BONE ARCHITECTURE: PERIPHERAL QUANTITATIVE COMPUTED TOMOGRAPHY AND QUANTITATIVE COMPUTED TOMOGRAPHY

Preamble

This section specifically describes the use of peripheral quantitative computed tomography (pQCT) and quantitative computed tomography (QCT) imaging of the lower extremity for the purpose of diagnosing osteoporosis and monitoring therapy among adults with spinal cord injury (SCI). The section also describes

recommended metrics and psychometric properties for both technologies, including the precision and least significant change.

Background

The 2019 International Society of Clinical Densitometry (ISCD) position statement²⁴ details recommendations for use of bone density testing among individuals with SCI. This statement is limited to densitometry (dual-energy X-ray absorptiometry [DXA]) and does not address or discuss alternative technologies for assessment of bone density or bone quality. Although DXA is the most common measurement tool for bone health assessment in North America, it is not routinely available worldwide. Many regions, particularly in Europe, have routine access to pQCT instrumentation and not DXA. In addition, QCT analyses based on calibrated clinical CT scans are becoming increasingly common.

Context

pQCT and QCT provide 3-dimensional measures of bone that account for variations in bone structure and density. These measures have the potential to be less sensitive to positioning errors and may be better predictors of bone strength and possibly fracture risk. Some pQCT and QCT measures have better precision than DXA for monitoring response to therapy among adults with SCI because of the ability to detect changes in bone density and structure within specific regions or compartments.

Both pQCT and QCT technologies provide 3-dimensional information about the distribution of bone mineral within the measurement site. Although QCT can be used to measure large volumes (e.g., the entire knee), pQCT is limited to thin (1-3 mm) transverse regions of interest (ROIs). The commercially available pQCT devices come with a sliding gantry that can obtain slices along the femur and tibia metaphysis and epiphysis, as well as at sites along the tibia diaphysis (XCT 2000/3000 scanner; Orthometrix/Stratec, White Plains, NY). High-resolution pQCT (HRpQCT) is a newer research tool able to measure both cortical and trabecular bone microstructure (Xtreme CT; Scanco Medical AG, Brüttisellen, Switzerland). HRpQCT is emerging as an important tool for understanding age- and disease-related changes to bone structure. The enclosed recommendations do not

address HRpQCT measurement for individuals with SCI, however, because of an insufficient body of literature.

Recommendation

- 4.1 We recommend that, as an alternative to DXA, peripheral quantitative computed tomography (pQCT) or quantitative computed tomography (QCT) imaging of the lower extremity can be used for monitoring bone health in adults with SCI.

1B

Clinical Consideration

4.1

Most pQCT and QCT measures have precision values (root mean square coefficient of variation [RMS-CV]) of 2% or lower, making these tools sufficiently precise to measure clinically relevant changes in bone.

pQCT and QCT Measurement Site

Recommendations

- 4.2 We recommend that both trabecular and cortical sites of the femur and tibia be measured annually to monitor regional changes in bone density and quality.

1B

- 4.3 We recommend that QCT of the hip can be used for diagnosing osteoporosis among individuals with SCI in accordance with International Society of Clinical Densitometry (ISCD) guidelines.

1B

- 4.4 We recommend the following anatomical sites for pQCT measurement for individuals with SCI where feasible, moving from distal to proximal starting from a reference line placed at the talocrural joint (4% tibia) to the distal end of the lateral femoral condyle (4% femur): measurements at the tibia 4%, 38%, 66%; measurement at the femur 4%.

1B

- 4.5 We recommend the following anatomical sites for QCT measurement among individuals with SCI: proximal femur, distal femur, proximal tibia. It is essential that QCT regions of interest be clearly defined and reported according to published best practices and guidelines^{261,262}

1B

Rationale

Scans of many different anatomical sites can be acquired with pQCT. In general, the more distal sites are easier to measure than the more proximal sites because of challenges with patient positioning, lower extremity contractures and spasticity, and limits of the scanner gantry. Consequently, distal sites have better precision than proximal sites (especially at/above the knee) due to challenges with patient positioning and movement.²⁶³ Because pQCT is limited to single thin sections, epiphyseal sites (4% tibia, 4% femur, and occasionally 96% tibia) are generally used to measure trabecular bone (primarily trabecular volumetric bone mineral density [vBMD]), whereas diaphyseal sites (38% and 66% tibia) are used to measure cortical parameters (Figure 4.1 and Table 4.1). The rationale for these measurement sites is explained in detail by Cervinka et al.²⁶⁴ QCT is able to measure larger volumes of bone and has been used to measure both cortical and trabecular bone at epiphyses, metaphyses, and diaphyses. QCT data for individuals with SCI have been reported at the proximal femur and the knee (distal femur, proximal tibia).²⁶⁵⁻²⁶⁸

Figure 4.1. Lower extremity anatomical sites recommended by Stratec for peripheral quantitative computed tomography analysis (reprinted with permission from Cervinka et al., 2018).²⁶⁹

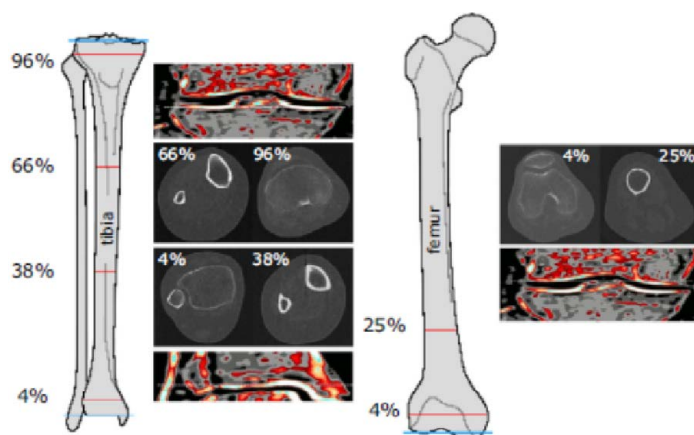


Table 4.1. Frequency of Measurement Sites in Reviewed pQCT Prevention/Therapy Studies

Measurement Site	Number of Publications	Study
4% tibia	12	Lala et al. 2014, ²³⁶ Shields et al. 2006, ²⁶⁹ Frotzler et al. 2008, ²⁷⁰ El-Kotob et al. 2020, ²⁷¹ Craven et al. 2017, ²⁷² Lambach et al. 2018, ²⁷³ Frotzler et al. 2008, ²⁷⁴ Frotzler et al. 2009, ²⁷⁵ Giangregorio et al. 2013, ²⁶² Eser et al. 2004, ⁶² Varzi et al. 2015, ²⁷⁶ Dudley-Javoroski et al. 2012 ²⁷⁷
38% tibia	6	Shields et al. 2006, ²⁶⁹ Frotzler et al. 2008, ²⁷⁰ Craven et al. 2017, ²⁷² Frotzler et al. 2008, ²⁷⁴ Eser et al. 2004 ⁶² , El-Kotob et al. 2020 ²⁷¹
66% tibia	6	Giangregorio et al. 2005, ²⁷⁸ Shields et al. 2006, ²⁶⁹ Giangregorio et al. 2006, ²⁷⁹ Giangregorio et al. 2013, ²⁶² Gibbs et al. 2018 ²⁸⁰ , El-Kotob et al. 2020 ²⁷¹
96% tibia	2	Coupaud 2015, ²⁸¹ Frotzler et al. 2008 ²⁷⁴
4% femur	7	Coupaud 2015, ²⁸¹ Frotzler et al. 2008, ²⁷⁰ Lambach et al. 2018, ²⁷³ Frotzler et al. 2008, ²⁷⁴ Frotzler et al. 2009, ²⁷⁵ Eser et al. 2004, ⁶² Varzi et al. 2015 ²⁷⁶
Other sites	9	Dionyssiottis et al. 2009, ²⁸² Frotzler et al. 2008, ²⁷⁰ Ashe et al. 2010, ²⁸³ Wuermser et al. 2015, ²⁸⁴ Giangregorio et al. 2006, ²⁷⁹ Dudley-Javoroski et al. 2012, ²⁷⁷ Frey-Rindova et al. 2000, ²⁸⁵ de Bruin et al. 2000, ²⁸⁶ de Bruin et al. 1999 ²⁸⁷

The measurement sites recommended herein are commonly reported in both able-bodied and SCI populations, and they represent a mix of cortical and trabecular regions. The 4% and 38% distal tibia regions have the shortest scanning time because of the small amount of soft tissue in this region. As a result, these are the easiest regions to obtain, as spasticity and clonus are less likely to interrupt scan acquisition. The 4% distal femur site is also recommended, as changes at the femur may be considerably different when compared with the tibia. However, this region may be difficult to image because of risk of movement from spasticity and problems with reproducible positioning of the leg. Recommended QCT and pQCT densitometric, shape, and strength metrics are based on the most clinically useful and validated metrics available. Trabecular and cortical vBMD and the bone strength index (BSI) provide densitometric and strength indexes at clinically relevant fracture sites; the ratio of bone mineral content (BMC) at 4% and 38% sites is a potentially important fracture risk indicator, and so may also be clinically relevant. Metrics from more proximal sites (i.e., proximal tibia, mid-femur) are less studied, have not been well-validated, and are not recommended at this time.

Of note, although there may be concerns related to the amount of radiation that is received by an individual during these measurements, the approximated radiation exposures associated with pQCT and QCT measurements are similar to those received during the DXA measurements. The values of approximated radiation exposure during different densitometry measurements are shown in Table 4.2. These values were abstracted from the 2007 ISCD Official Positions and review of radiation exposure in X-ray-based imaging techniques by Damilakis et al. 2010.²⁸⁹

Table 4.2. Approximate Radiation Exposures During Densitometry Measurements

Imaging Modality	Approximate Effective Dose (mSv)
Radiography	< 0.01
DXA	~ 0.01 – 0.05
Single-slice QCT	< 0.06 – 0.3
3D QCT scan	~ 1 – 1.5
pQCT	< 0.003
HRpQCT	< 0.005

Abbreviations: DXA, dual-energy X-ray absorptiometry; QCT, quantitative computed tomography; 3D, 3-dimensional; pQCT, peripheral quantitative computed tomography; HRpQCT, high-resolution peripheral quantitative computed tomography.

pQCT and QCT Metrics

Recommendations

- 4.6 We recommend that at a minimum the following metrics should be reported from pQCT:
- For trabecular sites (4% tibia and 4% femur): integral (also termed “total”) and trabecular volumetric bone mineral density (vBMD), cross-sectional area (CSA), and bone mineral content (BMC). If available, bone strength index (BSI) should be reported.
 - For cortical sites (38% and 66% tibia): BMC and CSA.
- 1B

- 4.7 We recommend that at a minimum, the following metrics should be reported from QCT: integral, cortical, and trabecular vBMD, BMC, CSA, and cortical thickness.
- 1A

Rationale

pQCT and QCT Metrics

In contrast to DXA, the 3-dimensional nature of pQCT and QCT can calculate metrics about bone structure and strength in addition to volumetric density measures (vBMD, in g/cm³) of the trabecular and cortical compartments within bone. These measures are highly correlated with the areal BMD (aBMD) metrics calculated with DXA (in g/cm²). Typical QCT metrics that are related to structural behavior include measures of CSA, moments of inertia, cortical thickness index (CTI), compressive strength index (CSI), and buckling ratio (BR).²⁶⁸ pQCT metrics include a subset of these measures, along with stress strain index (SSI)²⁷³ and BSI,²⁶⁴ both of which are density-weighted moment of inertia measures. A comparison of DXA, pQCT, and QCT recommended metrics is summarized in Table 4.3.

Table 4.3. Definitions of Metrics that Can Be Obtained With pQCT and QCT in Comparison to DXA

DXA Metrics	pQCT Metrics	QCT Metrics
DXA metrics (recommended by ISCD)	pQCT standard metrics (recommended)	QCT standard metrics (recommended)
aBMD (g/cm ²) - areal bone mineral density	vBMD (g/cm ³) - volumetric bone mineral density	vBMD (g/cm ³) - volumetric bone mineral density
BMC (g) - bone mineral content	BMC (g) - bone mineral content	BMC (g) - bone mineral content
T-score - standardized score comparing aBMD value to non-SCI young adult reference population (valid for adults >40 years)	CSA (cm ²) - cross-sectional area	CSA (cm ²) - cross-sectional area
Z-score - standardized score comparing aBMD value to non-SCI age-matched reference population	BSI (g*mm) - bone strength indexa	BSI (cm ³) - bending strength indexa
	CoTh (cm) – cortical thickness	Ct.Th (cm) - cortical thickness
	pQCT subregion designators	QCT subregion designators
	c – cortical	Ct - cortical
	t – trabecular	Tb - trabecular
	to - total (includes cortical and trabecular)	i - integral (equivalent to total)

Typical Changes in pQCT and QCT Metrics Associated With SCI

In the absence of intervention(s), the subacute phase of SCI, defined as less than 2 years of injury duration, is associated with rapid declines in bone mass of the

lower limbs. Losses in trabecular vBMD of 20% per year or more are consistently observed.^{265,277,286,292} In contrast, cortical vBMD changes very little,^{288,293-295} although some studies have noted declines in this variable and in total/integral vBMD.^{265,266,277} Following

acute SCI, cortical bone is rapidly resorbed from the endosteal surface, resulting in reductions in cortical bone volume, thickness, and mineral content.^{265,266}

These losses are structurally important and manifest as changes in structural measures such as the CTI, CSI, BR, SSI, and BSI.^{265,266} Differences in the anatomical site selected for observation (epiphyses/metaphyses vs. mid-diaphysis) between studies may partially explain the conflicting reports regarding declines in cortical bone.

In the absence of intervention(s), the chronic phase of SCI (≥ 2 years of injury duration) is associated with near steady-state measures of bone density and structure as shown by pQCT and QCT.^{275,296} Interventions during both the acute and chronic phases following SCI may affect both cortical and trabecular compartments. QCT and pQCT Metrics Are Highly Correlated with Other Standardized Measures (DXA)

QCT and pQCT Metrics Are Highly Correlated with Other Standardized Measures (DXA)

Since DXA-related measures of aBMD remain the gold standard for diagnosing osteoporosis, it is important to understand the relationship between them and pQCT or QCT measures of vBMD. However, because of differences in the specific measurement sites, only 1 study has directly compared DXA-derived aBMD values at the distal femur (DF) and proximal tibia (PT) with QCT measures at the same sites. In a cross-sectional validation study by McPherson et al.,²⁹⁷ based on the ROIs defined by Edwards et al.,²⁶⁶ aBMD was obtained by DXA and vBMD by QCT in 12 individuals with acute SCI and 34 individuals with chronic SCI. The validation findings revealed that all DXA and QCT data were highly correlated ($r \geq 0.93$).

In further support of the utility of QCT/pQCT to diagnose osteoporosis and predict fracture in individuals with SCI, Lala et al.²³⁷ performed DXA and pQCT measurements in a cohort of 70 individuals with SCI (19 of them with history of fracture). They found an increasing risk of fracture for every unit of standard deviation (SD) decrease in vBMD by pQCT. pQCT can detect differences in trabecular and cortical vBMD, strength measurements, and estimates of bone

stiffness and strength with the use of patient-specific finite element analysis. In a study by Tan et al., 2014,²⁹⁸ the authors observed that distal femur axial stiffness and maximal load were significantly lower in individuals with a history of fracture compared with those without prior fracture. When DXA and pQCT-derived metrics of BMC and strength (SSI) were compared between individuals with SCI and those in an able-bodied group, the SCI group had a significantly lower BMC and SSI.²⁸³ Furthermore, both SSI and BMC were correlated with the duration of injury.

QCT and pQCT Are Able to Detect Clinically Relevant Changes in Bone Density and Structure in Individuals with Acute SCI

QCT and pQCT metrics demonstrate longitudinal changes in individuals with acute (< 2 years after injury) SCI (Appendix E, Table 4B-1). In the only study that included matched DXA measurements, short-term changes in proximal femur strength were compared with changes in proximal femur aBMD in a case series that followed 13 men and women with acute SCI.²⁶⁶ Strength was estimated by using patient-specific finite element models that were generated from QCT images of the proximal femur. The rate of loss in the total proximal femur aBMD (2.2% per month) was 3-4 times lower than the rate of strength loss (6.9% per month). QCT data on the same subject cohort observed vBMC loss rates of 3.1% per month at the proximal femur²⁶⁵ (Appendix C, Table 4B-1). These data suggest that changes in aBMD measured with DXA may underestimate the actual loss in BMC and strength; they provide evidence that QCT measures are able to detect small clinically relevant changes in this patient population.

A number of studies report longitudinal changes after SCI by using only pQCT/QCT data. Although these studies do not include a direct comparison with DXA values, they provide additional evidence for the clinical utility of pQCT metrics. De Bruin et al.²⁹⁵ observed changes in tibia vBMD in 12 individuals with acute SCI over a 4-year period. They observed that, although all individuals lost a significant amount of bone (mean 40%), there was a high degree of variability (range 7.8%-83.5%). Varzi et al.²⁷⁷ performed serial pQCT

scans at the DF and PT regions in 25 individuals with acute SCI. They reported significant losses to PT total vBMD and a greater loss of vBMD in tetraplegics vs. paraplegics over a 12-month observation period. Others have reported similar ranges of bone loss, but have not observed that acute loss of bone density was related to injury level, gender, age, activity level, or spasticity.^{282,286} CoupauD²⁹⁹ noted a 20% decrease in PT and a 15% decrease in DF trabecular and total vBMD over a 12-month period, with similar changes occurring at the tibial and femoral diaphysis cortical regions. Similarly, Edwards et al.²⁶⁶ observed significant losses in cortical bone volume and BMC at DF and PT sites over a 3.6-month observation period in 13 very recently injured individuals (injury duration 2.2 months). Loss of cortical bone volume and BMC, but not vBMD, indicates that cortical bone is predominately lost through endosteal resorption. Collectively, this work suggests that loss of bone mass in the cortical diaphysis, where the predominant bone mass is located, occurs at approximately the same rate as trabecular bone in the epiphysis, findings that contrast with reports that cortical vBMD is lost at a slower rate.

pQCT and QCT measures are able to detect intervention effects. Functional electrical stimulation (FES)- and neuromuscular electrical stimulation-assisted standing in individuals with acute SCI can significantly decrease the rate of trabecular vBMD loss at the PT over a 3-year period.^{293,294} In contrast, standing in a standing frame and treadmill walking had little effect on pQCT metrics after 6 months.²⁸⁸ In addition, in a small study (n=5), body weight-supported treadmill training elicited inconsistent changes in bone geometry after 6-8 months.²⁷⁹

In summary, pQCT and QCT measures that describe cortical and trabecular bone density and mass, as well as bone strength metrics, decrease significantly during the first 2 years after SCI. These metrics are highly correlated with changes in more standard DXA measures (aBMD) and may reflect clinically important loss of bone that is not apparent with DXA. The effects of clinical interventions aimed at reducing loss of bone mass or structure in individuals with acute SCI can be detected with pQCT or QCT metrics. Although some studies demonstrate that changes can be detected

in intervals as short as 4 months, changes are most consistently observed over 12-month intervals.

Precision Measurement and Least Significant Change

Recommendations

- 4.8 We recommend that monitoring be performed when expected changes are greater than the individual least significant change of the measurement method. For general monitoring, measurements may be performed annually. Because cortical or trabecular compartments may change somewhat independently, it is important to monitor multiple sites (see 4.4 and 4.5) and to assess and report measurement precision.

1A

Clinical Consideration

4.8

Chronic injury is associated with near steady-state values for bone. In individuals with chronic injury (injury duration > 2 years), we recommend that measurements be performed annually. We recommend that measurements may be performed more frequently in individuals with acute SCI if a large time or treatment effect is anticipated. Acute injury is associated with large changes to vBMD at trabecular sites and BMC and to bone volume at cortical sites. Interval changes can be detected at 4-6 months during the acute phase. QCT or pQCT measurements may be performed more frequently in individuals with acute SCI or if a large time or treatment effect is anticipated.*

*Precision assessments are reported as the root mean square coefficient of variation (RMS-CV, typically expressed as a percentage).

- 4.9 We recommend that measurement precision be assessed and reported for each outcome metric as root mean square coefficient of variation (RMS-CV).

1A

Clinical Consideration

4.9

Precision assessments are reported as the RMS-CV (typically expressed as a percentage).³⁰⁰ For pQCT that only includes a single image slice, patient positioning is a major source of imprecision; therefore, precision studies should include repositioning and rescanning. This is less of a concern in QCT, where the analysis region is selected after the scan.

The ISCD guidelines on QCT³⁰¹ report that QCT precision is similar between studies that did and did not include repositioning/rescanning. Precision may differ between able-bodied and individuals with SCI because of wider variation in bone parameters within the SCI population. Therefore, precision should be assessed within an SCI population.

For pQCT, same-day repositioning and rescanning should be performed for precision measures. For QCT, scan reanalysis without repositioning and rescanning may be used to calculate RMS-CV when rescanning is impractical. Precision studies should be performed on individuals with SCI and should include 30 degrees of freedom in accordance with ISCD guidelines.

Steady-state values were also observed in a group of 70 individuals with chronic SCI (mean injury duration 15 years, SD 10 years).²⁹⁶

Several clinical trials in individuals with chronic SCI have used QCT or pQCT metrics as outcomes. Using QCT at the knee (distal femur, proximal tibia), Morse et al.²⁶⁸ observed 12-month improvements to distal femur cortical bone volume, CTI, and BR in 10 individuals who participated in FES-assisted rowing and were administered zoledronic acid, compared with 10 who only participated in FES-assisted rowing. Edwards et al.²⁶⁷ evaluated the efficacy of 12 months of teriparatide and mechanical stimulation, both separately and together, to increase bone mass and strength in 61 individuals with chronic SCI. Although the authors concluded that the interventions failed to provide any clinically meaningful improvements to bone mass or strength at the knee region, the study was well powered to detect clinically important changes. A smaller study (n=14 participants) also failed to detect treatment effects of body weight-supported treadmill training after 12 months.²⁸⁰

Shorter duration studies (<12 months) were not generally associated with detectable changes to bone. For example, Craven et al.²⁷³ did not observe changes in bone strength metrics after 4 months of FES-assisted walking or conventional therapy. Ashe et al.³⁰² reported variable effects after 6 months of FES-assisted cycling in a small case series. Similarly, mechanical vibration had little effect on either PT vBMD or hip aBMD in the lower extremities at 6 and 12 months.²⁸⁵ However, Lambach et al.³⁰³ reported that FES strength training followed by FES-assisted rowing produced 9-12 month changes to bone that were proportional to the stimulus delivered. In other studies, changes to 4% DF vBMD were not detectable after 6 months, but were significant after 12 months of FES-assisted cycling²⁷⁵ and were preserved after 12 months of detraining.³⁰⁴ In summary, pQCT and QCT measures that describe cortical and trabecular bone, as well as bone strength metrics, change very little in individuals with chronic SCI. Specific variables reach a steady state between 3 and 8 years after injury. These measures may detect the effect of interventions. However, many studies included in the literature are underpowered or are too short in duration (under 12 months) to detect treatment effects.

Rationale

QCT and pQCT Detect Clinically Relevant Changes in Bone Density and Structure

QCT and pQCT measures have been used to document longitudinal changes and detect treatment effects in several groups of individuals with chronic SCI (Appendix C, Table 4B-2). In a longitudinal study that confirmed previous reports that a new steady state for bone is reached in the paralyzed limbs several years after acute SCI, Frotzler et al.²⁷⁵ used pQCT to measure vBMD at the DF at baseline and then at 15 and 30 months in 39 individuals with motor complete acute and chronic SCI (duration of injury between 0.9 and 34 years). The authors observed a new steady state 3-8 years after SCI, with the onset of the steady-state condition dependent on the bone region and the specific pQCT densitometric variable. The femur reached steady state more quickly than the tibia did, and the epiphyses more quickly than the diaphyses.

Precision for QCT and pQCT Data Vary by Site and Metric, but are Similar to DXA Measures

Several studies have demonstrated the precision error of QCT and pQCT bone densitometers in individuals with SCI (Appendix C, Table 4C). Using pQCT in 12 chronic SCI and 21 able-bodied participants, Giangregorio et al.²⁶³ reported the SCI group precision error (RMS-CV%) for standard BMD and geometry variables of <2%, with the exception of total area (2.7%) and trabecular density (2.3%). In a similar study that included 7 individuals with SCI, Eser et al.³⁰⁵ reported CV% between 0.5% and 2.2% for vBMD at the distal tibia and femur epiphysis (4% region) and between 0.3% and 0.5% at the distal femur diaphysis. With QCT at the femoral neck, CV% for total, trabecular, and cortical vBMD ranged from 0.3% to 2.7%.²⁶⁵ A more recent study compared the CV% of 3 different post-acquisition software programs to segment bone marrow density and bone marrow area at the distal tibia region in 19 adults with SCI, 18 young adults, and 47 older adults.²⁸¹ In all 3 groups, the precision for bone marrow density was poor (CV: 10.9%-28.5%, depending on the software and group). Precision for detecting bone marrow area was better (CV: 1.9%-2.6% for SCI and young adults, but 4.3%-5.1% for older adults).

For pQCT, densitometric precision measures are generally less than 2%. Strength indices and shape metrics along the tibia (4% and 66%) range from 0.9% to 10.5%. When best practices are applied, QCT densitometric and shape metrics CV range from 0.3% to 2.7%.

Sources of imprecision include patient positioning, scanning and analyzing the correct ROI, movement artifact, variability in X-ray beam intensity, and variations in image analysis. Metrics of total and cortical area, cortical thickness, and circumference from pQCT have lower precision (RMS-CV 2.9%-10%) and should be interpreted with caution.

Reference Data

Reference data at various pQCT and QCT sites have been reported in able-bodied populations, but there are no established diagnostic criteria. Although T-scores are not immediately available at the measurement sites recommended herein, several studies in the tables in Appendix C (Tables 4A-4C) include able-bodied

reference populations. Furthermore, the broader research literature includes reports of pQCT metrics at these standard sites in a variety of populations, making it possible to identify diagnostic criteria. This continues to be a research need (see Section 9.0).

5.0 CALCIUM AND VITAMIN D₃: DIET OR SUPPLEMENTS

Preamble

This section describes the challenges in conducting nutritional intervention studies and highlights the role of dietary calcium, vitamin D, magnesium, protein, and supplements alone and in combination for preventing bone loss and treating osteoporosis among adults with spinal cord injury (SCI).

Context

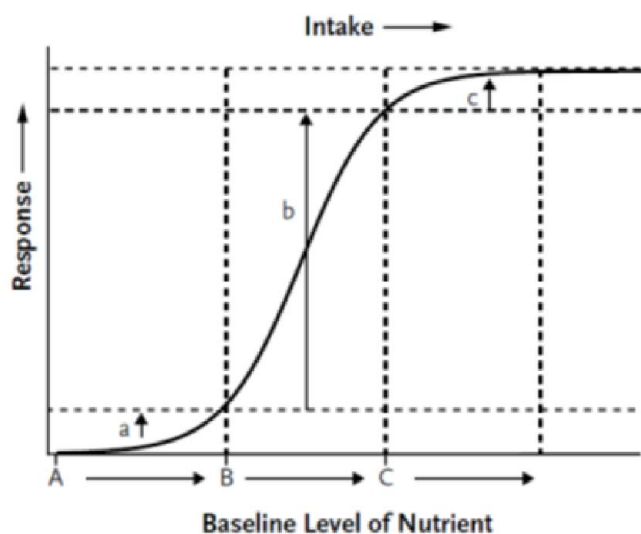
Evidence-based medicine, specifically randomized controlled trials, are of limited use to inform decisions about nutrition interventions,³⁰⁶⁻³¹³ and therefore nutrient interventions related to SCI and bone are difficult to interpret for the following reasons:

- Nutrient inadequacy is necessary to test the body's response to a nutrition intervention (one nutrient), whereas when a drug is tested to cure a disease, it is not the absence of the drug that has caused the disease.³⁰⁷ Nutrients affect many tissues, often within the "noise of biological variability," and such effects are often lost in clinical trials.³⁰⁷
- Nutrient effects follow a sigmoid-shaped curve,^{307,310,312} whereas drugs generally have responses in proportion to their dose. This means that with very low nutrient intakes or inadequate nutritional status, there is little response. In the middle ground, there is a larger response, but with high intakes or replete status, there is also little response (Figure 5.1). This means that in studies of nutrient supplementation, it is necessary to document nutritional status before the beginning of the intervention. Supplementation of a replete individual will likely have little effect.
- Nutrient effects are polyvalent, whereas drug effects are often more clear-cut and can be studied in isolation. An example is that calcium and vitamin D are intertwined in bone metabolism, making it difficult to study calcium or vitamin D alone.³¹²

- Nutrient effects may take years or decades to manifest themselves, whereas drug studies have relatively short outcome timelines.

Because the use of evidence-based medication trial guidelines is problematic for nutritional endpoints, alternative clinical trial designs must be applied to nutritional interventions in the SCI population.^{306,307,309} An example is the assessment of nutritional outcomes with a global index.

Figure 5.1. Intake response curve for a typical nutrient. The curve shows the response expected (a, b, or c) for the same intake of a nutrient at 3 different baseline levels (A, B, or C). For the same intake increment, a person with a baseline level of “A” has the response designated “a”; for baseline level “B”, the response is “b”, and so on (reproduced from Heaney, 2012³¹⁰).



Vitamin D3

Recommendations

- 5.1 We recommend that 25-hydroxyvitamin D (25-(OH)D) levels be repleted at least to a level of 80 nmol/L (32 ng/mL) in individuals with SCI and that maintenance doses of vitamin D₃ (cholecalciferol) of 25-50 mcg/day (1,000-2,000 IU/day) are reasonable in the SCI population. 25-(OH)D levels should be checked annually and 12 weeks following repletion therapy with a validated assay.

1B

Clinical Consideration

5.1

It is important to ensure that your laboratory is using a validated 25-(OH)D assay. Since most foods are not good sources of vitamin D, supplementation is generally required. Generally, retesting the 25-(OH)D level should be done no sooner than 12 weeks after a change in dose.³¹⁴ In the setting of vitamin D deficiency, consider using Figure 5.5 as a guide. typically expressed as a percentage).

Rationale

Introduction to Vitamin D₂ and D₃

Vitamin D is both a hormone, as it can be synthesized from 7-dehydrocholesterol, and a vitamin, because most populations do not synthesize enough vitamin D by the de novo pathway. Endogenous vitamin D (D₃) is synthesized from 7-dehydrocholesterol in the skin following ultraviolet-B exposure. The classic systemic route for vitamin D activation is initial hepatic 25-hydroxylation to 25-(OH)D via cytochrome P450-containing enzymes. In serum, 25-(OH)D is primarily bound to serum vitamin D binding protein and albumin, with less than 1% of total 25D circulating in its free (unbound) form.³¹⁵ Following 25 hydroxylation, there is renal conversion to the active 1,25-dihydroxy vitamin D (1,25-(OH)₂D) by cytochrome P450 family 27 subfamily B member 1. 1,25-(OH)₂D, known as the major bioactive metabolite, is the principal hormonal form of vitamin D. Its production is tightly controlled, being stimulated by parathyroid hormone (PTH) and inhibited by calcium, phosphate, and fibroblast growth factor-23. The actions of vitamin D are mediated through the stereospecific interaction of 1,25-(OH)₂D with the vitamin D receptor, a nuclear receptor and member of the steroid/thyroid receptor subfamily.

Vitamin D₂ (ergocalciferol) is not produced de novo by humans, but is found in plants, yeast, and supplements and thus can be a dietary source of vitamin D.³¹⁶⁻³¹⁸ Therefore, unless given daily, vitamin D₂ supplementation does not result in as high a blood level of 25-(OH)D as comparable amounts of vitamin D₃ (cholecalciferol).³¹⁹ Thus, despite earlier studies suggesting that vitamin D₂ and vitamin D₃ are equivalent,¹¹⁸ more recent work has called this into question, suggesting that vitamin D₃ may be the preferred supplement.^{320,321}

Importance of Vitamin D Assays

The accurate assessment of vitamin D and its metabolites is critically important. Liquid chromatography (LC)-tandem mass spectrometry is currently considered to be the most accurate and precise methodology for this assessment.^{115,322} Well-established risk factors for hypovitaminosis D include African American race, high body mass index, low nutritional and supplemental intakes, older age, and inadequate exposure to sunlight.³²³ In the able-bodied population without SCI, low serum 25-(OH)D levels lead to decreased intestinal calcium absorption, increased PTH secretion, and increased bone resorption.¹¹⁸ However, optimal levels of 25-(OH)D for skeletal and muscle health in the able-bodied population remain controversial. The Institute of Medicine suggests that persons are at risk for absolute vitamin D deficiency relative to bone health with serum 25-(OH)D levels below 30 nmol/L (12 ng/mL), with some, but not all, at risk for inadequacy at levels between 30 and 50 nmol/L (12 and 20 ng/mL).¹¹⁷ In contrast, the Endocrine Society considers serum levels of 25-(OH)D between 75 and 125 nmol/L (30-50 ng/mL) to be normal.¹¹⁸ One method that was widely used to establish normative data for 25-(OH)D is the level of 25-(OH)D in which PTH is suppressed into the normal range for most persons; this is approximately 50-100 nmol/L (20 to 40 ng/mL) in the able-bodied population.³²⁴

It is recommended that 25-(OH)D levels be checked in individuals with chronic SCI and that a validated assay be used.^{113-115,325-330} There are considerable issues related to which vitamin D metabolites should be evaluated and which assays should be used. The vitamin D External Quality Assessment program was started in 1989 and a vitamin D standardization program was founded in 2010^{114-116,327,328}; practitioners should understand whether their assay is covered under these quality assurance programs. For example, if an LC method is used, it should be assured that the 3-epi-25-OHD₃ metabolite (a metabolite of vitamin D₃ formed in the liver) is removed; with immunoassays, antibodies that have low affinity for 25-OH vitamin D could underestimate the total vitamin D content.¹¹⁵ Generally, LC-tandem mass spectrometry is considered the most accurate for the measurement of total vitamin D status.¹¹⁶ Because of problems with evaluation of 25-OH vitamin D₂ by immunoassays, it has been suggested that vitamin D₃ should preferentially be prescribed over vitamin D₂ and

that it is time to stop prescribing vitamin D₂. It should also be recognized that acute illness and surgery can lower 25-(OH)D results, and so the timing of vitamin D assessment is also important.³³¹ It is recommended that a 25-(OH) D level be rechecked 12 weeks after the beginning of repletion; since the half-life of vitamin D is approximately 1-2 weeks, this would represent 5 half-lives.³¹⁴

Determination of Adequate Vitamin D Status

Determination of adequate vitamin D status is complex. Criteria used to judge an optimal 25-(OH) D level include levels that maximally suppress the intact PTH level and levels that promote the greatest calcium absorption, a high bone mineral density (BMD), a low rate of bone loss, reduced fracture rates, and reduced rates of falling.³³² The estimates of optimal 25-(OH)D status have been complicated by issues with the vitamin D assay discussed earlier. One line of evidence considers the vitamin D status of traditional ancestral populations living outside in East Africa, which is reported to be 115 nmol/L.³³³ Current recommendations in individuals with metabolic bone disease suggest a target 25-(OH)D level of approximately 100 nmol/L (40 ng/mL).³³⁴ Our guidelines for vitamin D levels for individuals with SCI, described below, fall above those recommended by the Institute of Medicine for the general American public.^{335,336}

Intakes of Vitamin D and 25-OH Vitamin D Status in the SCI Population

Vitamin D is found in cold water fish, cod liver oil, eggs (approximately 1 mcg [40 IU] in 1 egg), beef and calf liver, fortified milk, and juice. It is often difficult for individuals to obtain adequate amounts of vitamin D from food sources alone, and so cholecalciferol (vitamin D₃) supplements are generally necessary to obtain adequate vitamin D intake³³⁷ (Table 5.1).

Investigations of vitamin D in the SCI population have generally been found to be deficient.³³⁸⁻³⁴¹ Hummel et al.¹¹⁹ completed a cross-sectional cohort study of 25-(OH)D levels, intact PTH, and serum C-terminal telopeptide of type I collagen (CTX) levels and the relationship between 25-(OH)D and intact PTH in men and women with chronic SCI. Of the study cohort, 39% had low 25-(OH)D levels and 13% had elevated PTH levels. There was a significant positive correlation between CTX levels and intact PTH levels,

suggesting that hyperparathyroidism was associated with bone breakdown. It was suggested that the threshold 25-(OH)D level to suppress intact PTH

levels may be higher in the SCI population than in the general population.¹¹⁹

Table 5.1. Sources of Vitamin D³⁴²

Food	Micrograms (mcg) Per Serving	International Units (IU) Per Serving	Percent DV ^a
Cod liver oil, 1 tablespoon	34.0	1,360	170
Trout (rainbow), farmed, cooked, 3 ounces	16.2	645	81
Salmon (sockeye), cooked, 3 ounces	14.2	570	71
Mushrooms, white, raw, sliced, exposed to UV light, ½ cup	9.2	366	46
Milk, 2% milkfat, vitamin D fortified, 1 cup	2.9	120	15
Soy, almond, and oat milks, vitamin D fortified, various brands, 1 cup	2.5-3.6	100-144	13-18
Ready-to-eat cereal, fortified with 10% of the DV for vitamin D, 1 serving	2.0	80	10
Sardines (Atlantic), canned in oil, drained, 2 sardines	1.2	46	6
Egg, 1 large, scrambled ^b	1.1	44	6
Liver, beef, braised, 3 ounces	1.0	42	5
Tuna fish (light), canned in water, drained, 3 ounces	1.0	40	5
Cheese, cheddar, 1 ounce	0.3	12	2
Mushrooms, portabella, raw, diced, ½ cup	0.1	4	1
Chicken breast, roasted, 3 ounces	0.1	4	1
Beef, ground, 90% lean, broiled, 3 ounces	0	1.7	0
Broccoli, raw, chopped, ½ cup	0	0	0
Carrots, raw, chopped, ½ cup	0	0	0
Almonds, dry roasted, 1 ounce	0	0	0
Apple, large	0	0	0
Banana, large	0	0	0
Rice, brown, long-grain, cooked, 1 cup	0	0	0
Whole wheat bread, 1 slice	0	0	0
Lentils, boiled, ½ cup	0	0	0
Sunflower seeds, roasted, ½ cup	0	0	0
Edamame, shelled, cooked, ½ cup	0	0	0

^aThe Federal Drug Administration developed DVs to help consumers compare the nutrient contents of foods and dietary supplements in the context of a total diet. The DV for vitamin D is 20 mcg (800 IU) for adults and children aged 4 years and older.³⁴³ The labels must list vitamin D content in micrograms per serving and have the option of also listing the amount in IUs in parentheses. Foods providing 20% or more of the DV are considered to be high sources of a nutrient, but foods providing lower percentages of the DV also contribute to a healthful diet. ^bVitamin D is in the yolk.

Adapted from Office of Dietary Supplements, National Institutes of Health.³⁴²

Optimal Levels of 25-(OH)D in the SCI Population

Information is limited on optimal levels of 25-(OH)D for skeletal and muscle health in individuals with SCI.

In 1 small study that included 62 individuals, Hummel et al.¹¹⁹ suggested that the threshold for 25-(OH)D for suppression of intact PTH is approximately 94 nmol/L

in SCI and that secondary hyperparathyroidism is associated with elevated bone resorption in this population. In support of this concept,¹¹⁹ others have also suggested that secondary hyperparathyroidism with vitamin D deficiency may contribute to the development of osteoporosis in SCI.^{120,121} In 1 study, high doses of vitamin D were needed to correct vitamin D deficiency levels.³⁴⁴

In individuals with SCI, if levels of 50 nmol/L (20 ng/mL) are used as the threshold to define vitamin D deficiency and 75 nmol/ L (30 ng/mL) to define suboptimal or insufficient vitamin D status,¹²³ conservatively, at least 1 in 3 individuals with SCI has a vitamin D deficiency.¹²¹ In 1 series,³⁴⁵ hypovitaminosis D as a secondary cause of osteoporosis was present in 2 of 3 individuals with SCI who were prescribed pharmacological treatment for osteoporosis. However, reports of the impact of hypovitaminosis D on skeletal and muscle health in SCI are limited. Low 25-(OH)D levels have been associated with markers of poor health in individuals with SCI, with positive associations with low testosterone levels,³⁴⁶ poor physical functioning, and low leisure time physical activity.³⁴⁷ In an observational cohort study that included 106 individuals, 25-(OH)D levels were not significantly associated with fall-related fractures.³⁴⁸ However, Bauman and colleagues³⁴⁹ reported a 0.021 g/cm² increase in lower extremity BMD after 12 months of vitamin D₂ intervention, and this increase remained stable over an additional 12 months. In athletes with SCI, 2 trials of short-term supplementation of vitamin D had small inconsistent effects on measurements of muscle strength.^{350,351}

Repletion of 25-OH in the SCI Population
There are safety concerns regarding vitamin D supplementation in SCI, in particular relative to nephrolithiasis. In some individuals, supplementation with vitamin D may cause hypercalciuria and an increased risk for renal stones. Hypercalciuria is defined as 24-hour urine calcium excretion greater than 250 mg/day (>6.24 mmol/day) in women and greater than 300 mg/day (>7.49 mmol/day) in men.³⁵² The frequency of hypercalciuria in individuals with SCI is highest in the first 3 months after injury and in those with complete injury.¹³⁰ Bauman et al.³⁵³ found that 2000 IU of vitamin D supplementation raised 25-OH vitamin D levels in individuals with chronic SCI.

Calcium

Recommendations

5.2 The following are recommendations for calcium intake as a combination of food and supplements (preference for dietary intake over supplements):

1B

Group and age	Calcium recommendation ^a
Men and premenopausal women age 19-50 years	1,000 mg/day
Men 50-70 years	1,000 mg/day
Women 50-70 years	1,000-1,200 mg/day
Men and women 71+ years	1,000-1,200 mg/day
pQCT	< 0.003
HRpQCT	< 0.005

^aNot appropriate for individuals who are found to be hypercalcemic.

Clinical Consideration

5.2
Dietary sources of calcium should be first optimized, and if a series of dietary interventions have failed, calcium supplements may be added to bring the person up to requirements. Dietary sources of calcium have a lesser impact on constipation in individuals with neurogenic bowel. Calcium supplements should not be used in the setting of hypercalcemia with acute SCI. Measurement of serum calcium levels is recommended prior to recommending calcium supplements. Consider using a calcium calculator to estimate dietary calcium intake (see the Resources for Patients subsection). When calculating calcium intake, it is important to consider all sources of calcium intake, including multivitamins and other mineral supplements.

5.3 One may consider a calcium intake of 750-1,000 mg/day from food and supplements for individuals with SCI and calcium oxalate stones, with a preference for dietary intake over supplements.

2D

Clinical Consideration

5.3

SCI-specific coexisting conditions such as bladder/renal stones must be taken into account by a clinician when instituting calcium supplementation. The choice of calcium dose (750 mg vs. 1,000 mg) is made on the premise that the individual would get at least 2/3 of their recommended dietary intake for calcium based on their age and sex. Following an oxalate-restricted diet is also recommended (Figure 5.4).

Rationale

Introduction to Calcium

Calcium is the most abundant mineral in the human body and bone contains calcium in the form of hydroxyapatite.³⁵⁴ Adequate calcium intake is important in the accrual of peak bone mass³⁵⁵ and is also important in the maintenance of BMD and in lowering fracture risk.³⁵⁶ Current adequate intakes for calcium are 1,000 mg/day for males and females aged 14-50, 1,000 mg/day for men aged 51-70, and 1,200 mg/day for women aged 51-70 and for men and women over the age of 70 years.³⁵⁴ Recent reports of moderate intakes of calcium contributing to cardiovascular risk and vessel calcification have not been substantiated.³⁵⁷⁻³⁶⁰ Table 5.2 shows sources and amounts of dietary calcium.

Table 5.2. Sources of Calcium in Food *

400 mg of calcium per serving
½ cup evaporated skim milk
½ cup dry milk powder
8 ounces of yogurt without added fruit
300 mg of calcium per serving
8 ounces of milk (any type of milk)
8 ounces of yogurt with fruit
8 ounces of calcium fortified orange juice
¼ cup Parmesan cheese
½ cup part-skim Ricotta cheese
1 ounce Swiss or Gruyere cheese

400 mg of calcium per serving

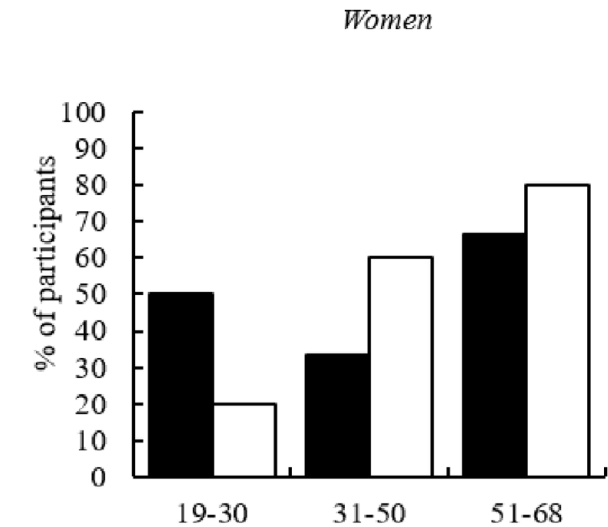
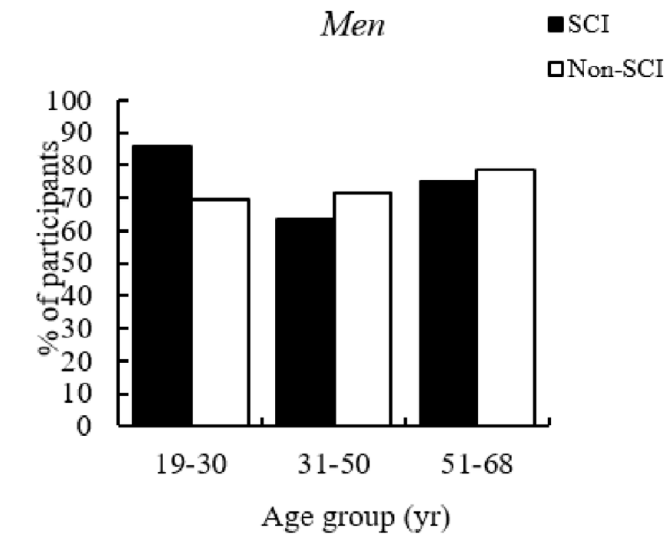
½ cup calcium-treated tofu
3 ounces of canned sardines with bones
200 mg of calcium per serving
1 ounce of natural cheese
150 mg of calcium per serving
½ cup pudding or custard
½ cup cooked collards
3 ounces of pink canned salmon with bones
100 mg of calcium per serving
1 ounce of nonfat cream cheese
½ cup turnip greens or bok choy
1 ounce almonds
½ cup cottage cheese
½ cup of ice cream, ice milk or frozen yogurt
½ cup white beans
1 serving of most calcium-fortified cereals
50 mg of calcium per serving
½ cup broccoli
½ cup kale or mustard greens
½ cup of most dried beans
1 medium corn tortilla
1 medium orange
1 tablespoon of dried milk

*Dairy products are the best sources of calcium, but calcium is also found in dark green leafy vegetables, dried beans and peas, and calcium-fortified juices and cereals. Adapted from <https://www.uab.edu/shp/toneyourbones/step-6-personal-treatment-plan/calcium-calculator>

Calcium Intakes in the SCI Population

Miyatani et al.³⁶¹ completed a cross-sectional observational study of nutrient intakes via a 24-hour dietary recall in individuals with traumatic SCI compared with intakes in age-, gender-, and weight-matched non-SCI individuals. Mean calcium intakes did not differ between the SCI and non-SCI participants. The Dietary Reference Intake recommendations for calcium were not met by 72% of the SCI participants and 73% of the non-SCI participants, as shown in Figure 5.2.

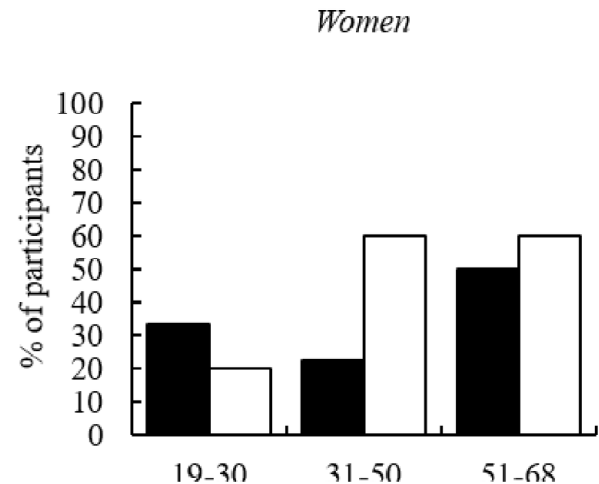
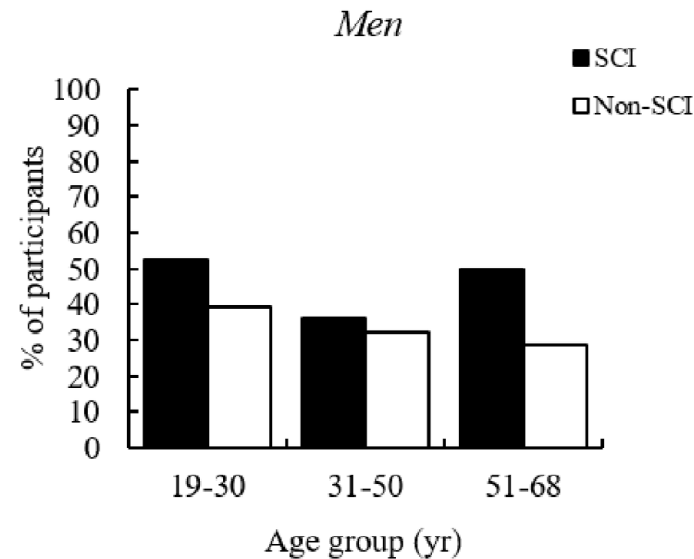
Figure 5.2. Percentage of individuals who consumed less than the adequate calcium intake by age group for spinal cord injury (SCI) and non-SCI participants.



Reproduced with permission.³⁶¹

Figure 5.3 shows the percentage of participants in each group who consumed less than 67% of adequate calcium intake.³⁶¹ Issues related to calcium supplementation in populations can include lactose intolerance, milk allergy from dairy foods, and constipation and gastrointestinal intolerance to calcium supplements.³⁶¹⁻³⁶⁴ Generally, calcium intake is first optimized from food sources and then supplements are considered if the individual’s intake remains

inadequate.
Figure 5.3 Participants in each group who consumed less than 67% of adequate calcium intake



Reproduced with permission.³⁶¹

Kidney Stones

Kidney stones are a rising global health problem,³⁶⁶ affecting 8.8% of the United States population³⁵² and a significant portion of those with SCI. The U.S. National Spinal Cord Injury Statistical Center reported that the incidence rate for renal calculi after the first year following SCI was 8 per 1,000 person-years.¹⁴⁴ Longer term follow-up of individuals with a traumatic SCI suggests that the cumulative proportion with renal calculi approaches 38% by 45 years.¹⁴⁵ The risk of developing a renal stone after SCI is between 7%

and 20% over a period of 8-10 years after injury.³⁶⁷ Moreover, the risk for recurrent renal calculi is substantial, with reported frequencies between 35% and 64% within 5 years.^{146,147} The prevalence of struvite stones has decreased with advances in urological care; however, staghorn calculi are common in individuals with SCI.¹⁴³ It is important to determine the type of stone before developing a treatment plan.

Chronic or frequent urinary tract infection is one of the most frequently cited risk factors for developing renal stones in the SCI population.^{143,367} Additional risk factors for stone disease include history of renal stone disease (hazard ratio 15, 95% confidence interval [CI] 7-38) or bladder stone disease (odds ratio 15.1, 95% CI 7.9-28.7),³⁶⁸ long-term use of an indwelling catheter,¹⁴³ and bone demineralization resulting in increased levels of urinary calcium.^{367,369}

Excess or restriction of certain minerals also affects stone development, and researchers have investigated several dietary interventions that target reduction of urinary calcium and oxaluria. In the general population, dietary salt restriction or adherence to a Mediterranean diet has been suggested to limit urinary calcium levels.^{370,371} Sufficient dietary calcium has also been shown to have a protective effect on stone formation, recommendations for daily intake ranging from 1,000 to 1,200 mg. Therefore, appropriate intake of vitamin D and dietary calcium does not cause kidney stones. Calcium oxalate stones comprise around 75% of renal calculi; in some cases, avoidance of high-oxalate foods is recommended.³⁷¹ The relevant literature among the general population with idiopathic hypercalciuria finds that long-term adherence (5 years) to diets that feature normal levels of calcium, low protein, and low salt may reduce stone recurrence.³⁷² Figure 5.4 shows recommended dietary modifications to restrict oxalate intake. In addition, in a non-SCI population, excess vitamin C is associated with stone formation, whereas magnesium lowers kidney stone formation.³⁷³ A combination of sodium/potassium citrate and magnesium oxide has been effective in inhibiting calcium oxalate stones.³⁷⁴

It is important to consider that these recommendations have been developed for those with idiopathic hypercalciuria and are not specifically targeted toward individuals with SCI. Therefore, it is essential to tailor dietary plans on an individual basis. Determining a balance between dietary calcium and oxalate intake is crucial; we recommend adequate hydration and adequate, but not excessive, calcium and oxalate intake as a means to reduce the risk of developing stone disease.

There are safety concerns regarding vitamin D supplementation in SCI, in particular relative to nephrolithiasis. In some individuals, supplementation with vitamin D may cause hypercalciuria and an increased risk for renal stones. Hypercalciuria is defined as 24-hour urine calcium excretion greater than 250 mg/day (>6.24 mmol/day) in women and greater than 300 mg/day (>7.49 mmol/day) in men.³⁵² The frequency of hypercalciuria in individuals with SCI is highest in the first 3 months after injury and in those with complete injury.¹³⁰ Moreover, in individuals with SCI, hypercalciuria is associated with elevated bone resorption.¹³⁰ Urinary calcium may remain elevated for up to 1 year following injury.¹³¹ However, restricting vitamin D intake can also increase the risk for renal stones.^{375,376}

Figure 5.4. Dietary modifications to reduce oxalate intake.³⁷⁷



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Risk of Bias and Lack of Nutritional Endpoints

Conclusion and Background of Suggested Guidelines

Seven relevant studies were identified and assessed for risk of bias prior to formulating our recommendations.^{53,378-383} Figure B5.1 in Appendix C displays the risk of bias and highlights opportunities for improving the rigor of the conduct of nutritional intervention studies in the SCI community.

The available literature does not provide conclusive evidence for calcium, vitamin D, or any other nutrients/supplements for bone outcomes in individuals with

chronic SCI because of the high risk of bias and the low quality of the literature. Magnesium and protein have not been specifically studied in the population with chronic SCI. Nutrition science and the associated methodological considerations were not taken into account in the available literature that was reviewed relative to this key question.³⁸⁴⁻³⁸⁸ The use of evidence-based medication trial guidelines is problematic for nutritional endpoints, and alternative clinical trial designs must be applied to nutritional interventions in the SCI population.^{384,386,389} An example is the assessment of nutritional outcomes with a global index.

Meeting established dietary guidelines for vitamin D and calcium is an area of concern in the SCI population, and emphasis should be placed on meeting Dietary Reference Intakes established by the Food and Nutrition Board.³⁹⁰ Numerous guidelines for calcium and vitamin D intake exist for individuals with metabolic bone diseases and are used as recommended guidelines in the SCI population. The International Osteoporosis Foundation recommends that calcium intakes from the Institute of Medicine be used as a guideline.^{117,195,337} However, in these guidelines, the Paralyzed Veterans of America panel has modified the calcium intake guidelines for individuals with SCI because of possible risk of kidney stones. It is important to remember that calcium and vitamin D supplementation must be considered in tandem.

In the absence of SCI-specific literature, ensuring adequate but not excessive intakes of calcium and vitamin D in accordance with guidelines for the general population is a rational approach. However, SCI-specific coexisting conditions such as immobilization hypercalcemia, stones, and intolerance to calcium must be taken into account by a clinician in instituting calcium and vitamin D supplementation.^{125,391}

Vitamin D

It is recommended that a 25-OH vitamin D level be checked in individuals with chronic SCI and that a validated assay be used.^{113-115,325-330} It should also be remembered that acute illness and surgery lower 25-OH vitamin D results.³³¹ There are considerable issues related to which vitamin D metabolites should be evaluated and which assays should be used. A vitamin D standardization program was founded in 2010 and the vitamin D External Quality Assessment program was started in 1989^{114-116,327,328}; practitioners should understand whether their assay is covered under these quality assurance programs. For example, if an LC method is used, it should be assured that the 3-epi-25D₃ metabolite is removed, and with immunoassays, antibodies that have low affinity for 25-OHD₂ could underestimate the total vitamin D

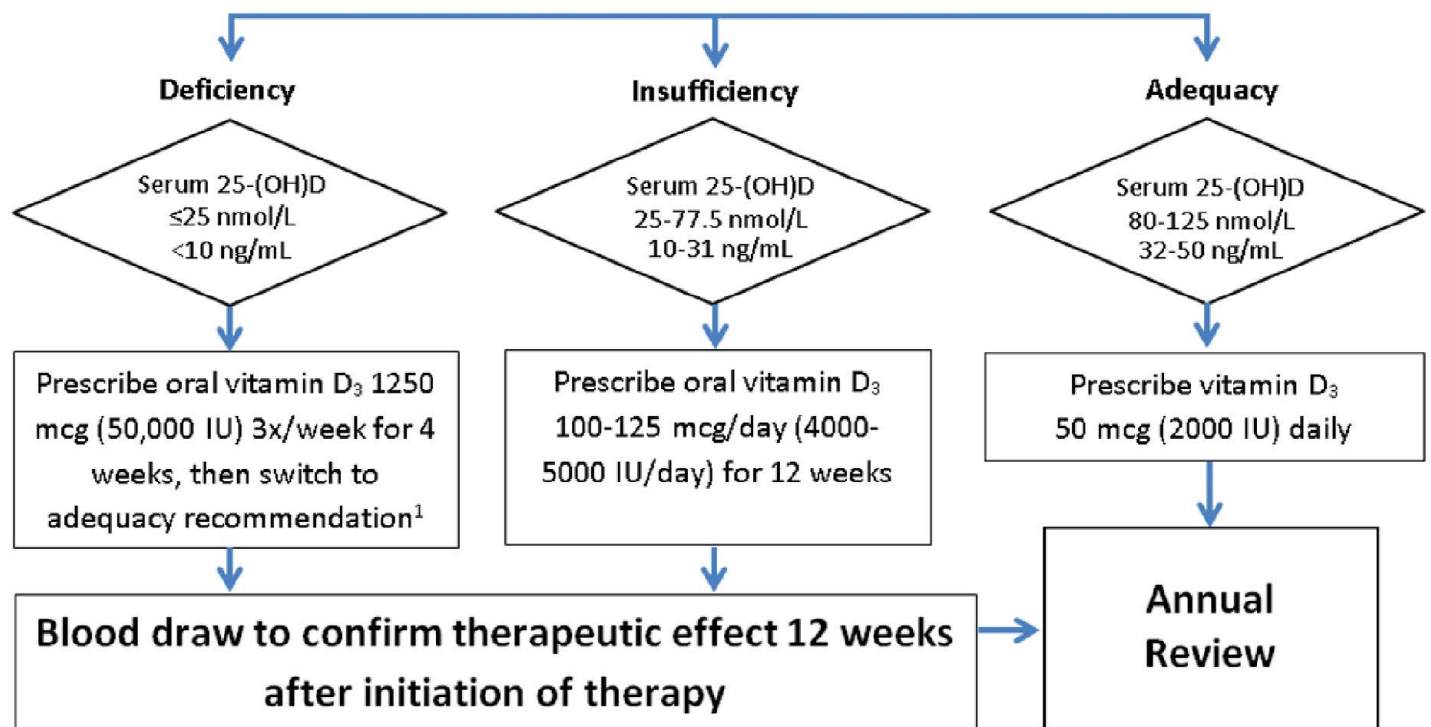
content.¹¹⁶ Generally, LC-tandem mass spectrometry is considered the most accurate for the measurement of total vitamin D status.¹¹⁶ Because of problems with evaluation of 25-OHD₂ by immunoassays, it has been suggested that cholecalciferol should preferentially be prescribed over ergocalciferol and that it is time to stop prescribing ergocalciferol.³⁹²

Maintenance therapy with 25-50 mcg (1,000-2,000 IU) of vitamin D₃ (cholecalciferol) is recommended per day,^{336,337} assuming that vitamin D status is adequate. A reasonable target for a 25-(OH)D level is 100 nmol/day (40 ng/mL).^{337,393} Vitamin D is found in cold water fish, cod liver oil, eggs (approximately 1 mcg [40 IU] in 1 egg), beef and calf liver, fortified milk, and juice (Table 5.1). It is often difficult for individuals to obtain adequate amounts of vitamin D from food sources alone, and so cholecalciferol supplements are generally necessary to obtain adequate vitamin D intake.³³⁷ Bauman et al.³⁵³ found that 2000 IU of vitamin D supplementation raised 25-OH vitamin D levels in individuals with chronic SCI.

In treating deficiency, generally, daily supplement repletion vs. large weekly doses is recommended because of the concern that, with larger doses, there is more 24-hydroxylation with the formation of inactive 24,25-(OH)₂D₃.^{394,395} There have also been recent concerns about large doses of vitamin D increasing the risk of falls in the general population.^{364,396,397} However, some literature supports the use of high-dose vitamin D therapy for vitamin D repletion (stoss therapy) in specific populations.³⁹⁸⁻⁴⁰⁰ Because of low levels of vitamin D in foods, treatment of insufficiency and deficiency generally requires the use of supplements.

The algorithm in Figure 5.5 is a suggested regimen for the treatment of deficiency and insufficiency and the maintenance of sufficiency. The 25-(OH)D categories for deficiency, insufficiency, and adequacy follow from the work of Heaney^{401,402} and the thresholds for adequacy are higher than those in the Institute of Medicine guidance for the general population.^{335,336}

Figure 5.5. Paradigm for vitamin D correction based on serum measures of 25-hydroxyvitamin D (25-(OH)D) and for maintenance of vitamin D status.⁴⁰⁰



Calcium

Calcium intake may be increased by increasing food sources of calcium (good sources include dairy foods, leafy greens except for spinach, legumes, and fish where the bones are eaten)⁴⁰³ or by taking calcium supplements in divided doses. There are several caveats to these calcium recommendations. In individuals with kidney stones, generally, the calcium intake should mainly come from food sources. If the stones are calcium oxalate stones, then a low-oxalate diet is recommended.⁴⁰⁴⁻⁴⁰⁶ In individuals with malabsorption such as malabsorptive bariatric surgery, intake may need to be greater and generally calcium citrate is recommended as the calcium supplement.⁴⁰⁷ Because renal stones often contain oxalate, moderation in oxalate intake is also recommended. Therefore, the final recommendation for individuals with SCI will be slightly different than will that for the general population because of the concern regarding kidney stones associated with high calcium and/or high oxalate intake.

Resources for Patients

Websites to Estimate Calcium Intake

<https://www.uab.edu/shp/toneyourbones/step-6-personal-treatment-plan/calcium-calculator>
<https://www.iofbonehealth.org/calcium-calculator>
<https://osteoporosis.ca/bone-health-osteoporosis/calcium-calculator/#page-1>

6.0 REHABILITATION THERAPY

Preamble

This section describes rehabilitation interventions (standing, overground walking, treadmill training, neuromuscular electrical stimulation [NMES], and functional electrical stimulation [FES]) that are appropriate for (1) prevention or (2) treatment of low bone mass, osteoporosis, and high fracture risk among individuals with spinal cord injury (SCI). The importance of loading and its assessment during rehabilitation is emphasized. Readers interested in assessing fracture risk prior to provision of rehabilitation therapy are directed to Section 1.0 (Medical History, Assessment of Fracture and Fall Risk), Section 3.0 (Bone Density: Dual-Energy X-Ray Absorptiometry), and the fourth

International Society of Clinical Densitometry Official Position²⁴ addressing the lack of established dual-energy X-ray absorptiometry (DXA)-based contraindications for rehabilitation therapy.

Context

Bone is a dynamic tissue, responding to increases and decreases in load across the lifespan. The mechanostat theory proposes that bone formation exceeds bone resorption when the bone receives intermittent forces that are above a “minimum effective strain.”⁴⁰⁸ External gravitational loading and muscle contractions are the 2 primary mechanical factors sensed within bone (e.g., fluid flow shear stress) that result in changes in the balance between bone formation and resorption.⁴⁰⁹ Other factors, including cytokines released by contracting muscle, may also influence bone cells directly, and cytokines released by bone tissue may interact with receptors within muscle (e.g., leptin and osteocalcin).^{410,411} Indeed, myriad factors are likely involved in the “cross talk” between muscle and bone with demonstrated role(s) in preventing or reversing bone mineral loss based on research in non-spinalized animal models of immobilization or bone tissue culture. Future research will likely reveal ways in which these factors may play a role in the bone mineral loss in humans after SCI⁴¹²⁻⁴¹⁵ as well. The purpose of this section is to examine whether loading during standing or walking, or local muscle contraction provided by electrical stimulation delivered peripherally, can be used to prevent, reduce, or treat low bone mass primarily caused by paralysis (American Spinal Injury Association [ASIA] Impairment Scale [AIS]-A, AIS-B, or AIS-C) after SCI.

Definitions

Standing and **walking** are common rehabilitation strategies following SCI when they are determined to be appropriate for the individual on the basis of level and completeness of the injury, the goals of the individual, and the overall plan of care.⁴¹⁶ **Passive standing**, in which muscle activation is unlikely, may be performed with individuals with SCI in a standing frame, standing wheelchair, long leg braces, or other devices.⁴¹⁷ **Active standing** refers to a more dynamic condition when standing involves some muscle activation, either by voluntary muscle contraction (e.g., in people with incomplete SCI) or by using FES/NMES (see definitions below). Walking⁴¹⁸ is recommended for maintaining or

increasing bone strength in the general population,⁴¹⁹ but may be an insufficient stimulus to improve or maintain bone health in certain medical conditions, such as SCI. Walking training may be performed overground or on a treadmill with varying amounts of body-weight support and voluntary muscle activation to achieve different levels of loading. Overground training may include orthoses,^{417,420} exoskeletons,⁴²¹ assistive devices,⁴²² supportive harnesses, or other devices, depending on individual needs. These interventions may be progressed through the use of less supportive assistive devices and decreased support of orthoses/exoskeletons/harnesses. Walking training on a treadmill may include body-weight support, the goal being to increase loading over time as walking improves,⁴²³ or robotics to provide or guide movement patterns.⁴²⁴ Specific training protocols, such as locomotor training, may also seek to target spinal locomotor pattern-generating circuitry in attempts to improve recovery of locomotor function.⁴²³ Whether these training interventions also confer a bone health benefit has been examined in a few studies, which are reviewed here.

Neuromuscular electrical stimulation (NMES) is defined as the application of an electrical current of sufficient intensity to elicit muscle contraction.

Functional electrical stimulation (FES) refers to the process of pairing NMES simultaneously or intermittently with a functional task, such as cycling or rowing. NMES and FES have the potential to positively affect bone as mechanical loading influences bone mass and structure and muscle contraction can create large physiological loads on bone.⁴²⁵⁻⁴²⁹ Although not included as evidence for outcomes in this clinical practice guideline (CPG), studies in animal models can provide insight into bone changes that may occur clinically. For example, in a rat model, Qin et al.⁴³⁰ demonstrated that NMES could improve muscle morphology and may potentially affect bone in a positive manner as evidenced by reduction in markers of bone resorption and increased genetic signals (mRNA) that precede increases in bone formation.

Loading

With all of these aforementioned interventions, the intention is to cause repeated **loading** of the musculoskeletal system^{431,432} in order to improve bone mineral density and quality. The therapeutic benefits of such exercise are thought to be a result of the

cumulative load or the sum total of multiple loading cycles. Thus, a given activity has a maximum force that is produced and a number of times that it is produced, which, collectively, dictate the **cumulative load**. The concept of using total work (e.g., watts during cycling/rowing) reflects this construct. Although a minimum effective strain on bone is needed for positive bone adaptations,⁴³³ it is not feasible clinically to measure this loading as it relates to the strains/forces received by cells within bone tissue. Therefore, surrogate measures have been developed in efforts to estimate loading on bone. Currently, there are no standardized measures for describing load, and researchers report estimates of loading that are based in part on the intervention used. We provide information on bone loading as reported by the authors of papers reviewed, whenever available. Loading estimates reported in the literature are described in a variety of ways: quantity of external weight lifted during leg extensions, total work during leg cycling or during leg and arm rowing (watts), biomechanical model-based estimates of loading when using electrical stimulation during standing, and total distance rowed. Power output measures will not specify load at a particular joint, and in the case of FES rowing,⁴³⁴ power output reflects the total work of both the arms and the legs. For standing trials, load on a particular joint may be estimated by using body segment models or as the force “off-loaded” during electrically induced muscle contraction.^{293,435,436}

In addition to standing, walking, treadmill training, NMES, and FES, the effect on bone mineral density (BMD) of some general exercise programs have also been examined.⁴³⁷⁻⁴⁴⁰ However, the variable methodology within and among these studies does not allow any conclusions to be drawn. Two systematic reviews on the effects of exercise^{441,442} found a high risk of bias and inconsistent results for the effects on BMD. Thus, studies that examined a general exercise program are excluded from this CPG.

Individuals who meet the following criteria are appropriate candidates when considering standing, walking, NMES, or FES interventions:

- Acute or chronic SCI
- AIS-A, B, C, or D
- Ability to tolerate and engage in electrical stimulation-based therapy if the use of NMES or FES is desired

Specific to bone health, individuals with a non-union fracture or substantial bone alignment abnormality should be excluded from these therapies. Clinicians need to also consider other precautions and contraindications specific to the activity being performed and the potential risk of injuries during these activities.

Therapeutic Considerations Prior to Initiating Rehabilitation Therapies

- A review of concurrent medical therapies with potential adverse effects on bone mass accrual and fracture risk are recommended prior to initiating exercise therapy.
- An assessment of non-BMD risk factors for fracture should be done to inform the individual with SCI regarding the potential risks and benefits of exercise intervention therapy (see Section 1.0).
- Concurrent provision of an adequate, but not excessive, dietary calcium intake and maintenance of optimal serum 25-hydroxyvitamin D serum and parathyroid levels are recommended (see Section 5.0)

Prevention of BMD Decline

Throughout Sections 6.0 and 7.0, interventions to prevent the onset of low bone mass or sublesional osteoporosis are discussed. These are interventions that are typically offered early post-injury when the individual's bone mass has not yet been adversely affected by their spinal cord impairment, where one aims to ameliorate or prevent excessive resorption of hip and knee region bone mass and promote bone formation.

Passive Standing

- 6.1 One may consider passive standing for 1 hour 5 times per week for at least 2 years to reduce BMD decline at the hip and knee regions.
- 2D

Clinical Consideration

6.1

There are other therapeutic benefits of standing beyond the scope of this CPG.^{15,443}

Rationale

Few studies have examined the effect of standing on prevention of BMD loss, and those that have, primarily conducted with individuals with AIS-A and AIS-B SCI, have shown mixed results. These studies score low on quality, mainly due to uncertainties or high risk of bias in study design, selection criteria, and outcomes assessed (see Appendix E, Figures B6.1 and B6.2). The largest study was observational, with 26 individuals who started passive standing during their initial inpatient hospitalization. Decreases in the rate of BMD loss in the lower extremities and pelvis were seen after 2 years of passive standing for 1 hour, 5 times per week, compared with that of a non-standing group.⁴⁴⁴ However, there were no between-group differences in BMD loss at the 1-year time point. A small randomized controlled trial (RCT) of 3 groups (standing only, standing + treadmill training, non-standing control) found decreases in the rate of BMD loss in tibial trabecular but not cortical bone for 5 individuals who stood for >5 hours per week for 25 weeks. The decreased rate of BMD loss was comparable to that of a combined standing/treadmill training group, whereas individuals in the non-standing group experienced declines in BMD.⁴⁴⁵ Two other studies included a passive standing group as a control group (n=19), but either did not analyze BMD results for the standing group separately⁴⁴⁶ or did not include a non-treatment control group for comparison.⁴⁴⁷ One cross-sectional study was excluded from this CPG because of the lack of baseline BMD measures.⁴⁴⁸ Therefore, there is low or very low-level evidence that passive standing may reduce BMD loss after SCI (Level 2D evidence).

Overground Walking

Rationale

No studies that examined prevention of BMD decline by using walking as an intervention met the criteria for this CPG. Since walking is recommended for maintaining or improving bone health in the general population, it is encouraged for those who are able to do so after SCI. However, consideration should be given to reducing risk of falls and related possible fracture in individuals with incomplete SCI and poor balance or leg muscle strength.

Treadmill Training

Rationale

At this time, there is weak evidence demonstrating that treadmill training prevents a decline in BMD at the hip and knee regions. Limitations in methodology further limit our ability to make a recommendation at this time. Only 2 studies were reviewed that explored the effect of treadmill training on prevention of bone loss. One small RCT found a decreased rate of BMD loss in tibial trabecular but not cortical bone for the 4 individuals with AIS-A or AIS-B SCI who performed a combined intervention of standing and body-weight-supported treadmill training (ranging from 20% to 80%, mean 40%) for >5 hours per week for 25 weeks.⁴⁴⁵ The decreased rate was the same as that of a standing-only group, whereas individuals in the non-standing group experienced declines in BMD, although it is unclear how individuals were assigned to each group (see Appendix E, Figure B6.3). In contrast, another small study with individuals with AIS-B (n=4) or AIS-C (n=1) SCI provided body-weight-supported treadmill training for 48 sessions 2 times per week for 6-8 months and found no changes in BMD or in bone biochemical markers.⁴³² The percentage of body-weight support at baseline (mean 84%, SD 17%) decreased by midpoint (mean 47%, SD 28%) at 24 sessions and decreased further by 48 sessions (mean 42%, SD 29%).

Functional Electrical Stimulation and Neuromuscular Electrical Stimulation

Recommendations

- 6.2 We suggest lower extremity functional electrical stimulation (FES) or neuromuscular electrical stimulation (NMES) as an option for preventing BMD decline in the hip and knee region. The most effective FES and NMES interventions should include the following:
- 6.2.1 We recommend that FES delivery create a visibly strong contraction against some resistance during some functional task, such as cycling or rowing, using appropriate stimulation parameters to create lower limb muscle contractions (e.g., pulse durations of 200 μ s or higher, frequencies of 20-33 Hz, and amplitudes up to 140 mA), for at least 30 minutes, 3-5 days per week, for at least 1 year.

1D

- 6.2.2 We recommend that NMES delivery create a visibly strong contraction against some resistance, such as an isometric contraction or movement against gravity or during loading, using appropriate stimulation parameters to create lower limb muscle contractions (e.g., pulse durations of 200 μ s or higher, frequencies of 20-33 Hz, and amplitudes up to 140 mA, but the effective stimulation parameters may vary among individuals), for at least 30 minutes, 3-5 days per week, for at least 1 year.

1B

Clinical Consideration

6.2

NMES should be delivered in weight-bearing standing that creates an extensor muscle contraction that offloads a portion of body weight, gradually increasing the active muscle contractions to provide greater weight support from muscle contraction rather than the standing frame, as tolerated.

Physicians and researchers should assess BMD at sites that have the potential to be affected by the FES and NMES intervention and not at a remote site.

Exercise caution when providing FES and NMES interventions to individuals with chronic SCI, low bone density, and a number of non-BMD risk factors for fracture in order to mitigate fracture risk.

Electrical stimulation-based therapy should be prescribed and/or implemented only by clinicians with expertise in electrical stimulation and SCI.

9-12 months has the potential to prevent BMD decline at the distal femur and tibia. If follow-up was less than this time period, differences in BMD were not observed.²⁴⁶ Generally, risk of bias was considered low in these studies, although there were questions around selection and analysis methods (see Appendix E, Figure B6.5).

There is moderate-level evidence that a muscle contraction against some resistance is needed to decrease the rate of BMD loss after SCI. There is high-level evidence that BMD changes occur preferentially at the bone sites where muscle contractions generate forces on bone (i.e., muscle origins and insertions) and not at remote bone sites unaffected by the intervention.

Neuromuscular Electrical Stimulation

There is low-level evidence that a muscle contraction against some resistance is needed to attenuate BMD decline. There is low-level evidence that NMES interventions should be performed for at least 30 minutes, 3-5 days per week, for 12 months to attenuate BMD decline. Investigators are encouraged to provide greater detail on participant selection, group allocation and concealment, and blinding of assessors to strengthen the level of evidence supporting NMES as an effective therapeutic modality to attenuate BMD decline (see Appendix E, Figures B6.6 and B6.7).

There is moderate-level evidence that BMD decline can be attenuated when NMES is delivered during passive weight bearing through the lower extremities in an erect posture with a load of approximately 70%-150% of body weight.⁴⁴⁹ These values were based on body segment modeling and may be difficult to measure or achieve clinically, which is why the recommendation is to use electrical stimulation to offload a portion of body weight by using muscle contraction. Progression is recommended as tolerated as muscle strength increases or as muscle fatigue decreases with training.

There is high-level evidence that BMD changes will be observed only at sites that have the potential to be affected by the intervention and not at a remote site.

Rationale

Functional Electrical Stimulation

There is low-level evidence (2 primary prospective studies, nonrandomized) that performing quadriceps and hamstrings FES (cycling or rowing for 2.5 to 5 hours per week in 3-5 sessions) for a minimum of

Treatment of Low BMD

Passive Standing

There are many therapeutic benefits of standing beyond the scope of this CPG.^{15,443} There is no evidence that passive standing is effective for treatment of bone loss in chronic SCI. To date, there are no adverse effects reported to be associated with passive standing, suggesting risks are low. One study with a relatively low risk of bias (see Appendix E, Figure B6.8) examined treatment of low BMD by using standing interventions with individuals with AIS-A and AIS-B SCI. In this observational study, 60 individuals either did not stand or stood for variable amounts of time (<1 hour per day or >1 hour per day) over 1 year by using a standing frame, standing wheelchair, or crutches and orthoses.⁴⁵⁰ No changes were seen in proximal femoral BMD in any group. Another small study had individuals use a standing frame, but results for those with SCI could not be separated from those with multiple sclerosis, and so the study was excluded from this CPG.⁴⁵¹

Overground Walking

There is weak evidence and are limitations in the methodology for demonstrating the effects of walking training on increasing hip and knee region BMD. Two small (n=4 or n=7 participants) very low-quality observational studies (see Appendix E, Figure B6.9) examined the effects of walking with reciprocating gait orthoses for 2-3 hours per day, 3-7 days per week, for 3-30 months for individuals with paraplegia of unknown AIS classification.^{452,453} In Ogilvie et al.,⁴⁵⁴ results were provided in a case-series format that showed mixed results for hip BMD without a statistical analysis being performed after 18-30 months of walking. In the other study (Thoumie et al.⁴⁵⁵), statistical analysis showed mixed results, with significantly decreased femoral neck BMD in 4 of 7 participants after 3-14 months of walking.

Treadmill Training

At this time, there is weak evidence and limitations in the methodology for demonstrating the effects of treadmill training on increasing BMD. For treadmill training, 1 small low-quality study (see Appendix E, Figure B6.10) with individuals with chronic AIS-B and AIS-C SCI reported no changes in BMD or bone geometry across several sites following body-weight-

supported treadmill training performed for up to 45 minutes, 3 times per week, for 12-15 months.⁴⁵⁶ Proximal and distal femur, proximal tibia, spine, and whole-body sites were tested by DXA and bone geometry, and mid-femur and proximal tibia sites by computed tomography. Although BMD did not increase, it did not decrease at common sites for fracture in SCI, suggesting it might be able to help maintain BMD in chronic SCI.

Functional Electrical Stimulation and Neuromuscular Electrical Stimulation

Recommendations

6.3 We suggest lower extremity FES or NMES as an option for treating low BMD in the lower limbs. The most effective FES and NMES interventions should include the following:

6.3.1 We recommend that NMES delivery create a visibly strong contraction against incrementally increasing resistance, such as an isometric contraction or movement against gravity or during weight bearing, using appropriate stimulation parameters to create lower limb muscle contractions (e.g., pulse durations of 200 μ s or higher, frequencies of 20-33 Hz, and amplitudes up to 140 mA have been reported, but effective stimulation parameters may vary among individuals), for at least 30 minutes, 3-5 days per week, for at least 1 year.

1B

6.3.2 We recommend that FES delivery create a visibly strong contraction against incrementally increasing resistance, using appropriate stimulation parameters to perform some functional task (e.g., pulse durations of 200 s or higher, frequencies of 20-33 Hz, and amplitudes up to 140 mA have been reported, but effective stimulation parameters may vary among individuals), for at least 30 minutes, 3-5 days per week, for at least 1 year.

1D

Clinical Consideration

6.3

NMES should be delivered to offload a portion of body weight by using muscle contraction. Progression is recommended as tolerated as muscle strength increases or as muscle fatigue decreases with training.

Physicians and researchers should assess BMD at sites that have the potential to be affected by the FES and NMES intervention and not at a remote site.

There is high-level evidence (multiple controlled and uncontrolled primary observation intervention studies) that FES training of low intensity (e.g., FES cycling at a power output of <18 W) is insufficient to allow bone changes to occur, as shown by an absence of significant changes in BMD.^{284,446,459,469,470}

There is high-level evidence that weekly training volumes of fewer than 2.5 sessions per week are insufficient to allow bone changes to occur, as shown by an absence of significant changes in BMD.^{284,464,465,467}

There is high-level evidence (controlled and uncontrolled primary observation interventions) that neither FES treadmill gait training twice per week at 20 minutes per session for 6 months, nor FES ambulation 3 times per week for 11-19 weeks, is sufficient to improve BMD in the proximal femur.^{467,468}

There is moderate-level evidence (observational studies, nonrandomized) that performing quadriceps FES cycling or FES standing for 3-5 hours per week (in 3-5 sessions) for a minimum duration of 9 months can partially reverse bone mineral loss at the distal femur and proximal tibia.^{446,459-461}

Recommendation

6.4 We suggest that a minimum duration of 1 year for lower extremity muscle-activated and load-bearing rehabilitation therapy is needed before an effect on bone density is expected. Further, to maintain effects on bone density, lower extremity muscle-activated and load-bearing rehabilitation therapy needs to be continued indefinitely.

1B

Overall, of the 15 studies reviewed, 4 demonstrated a positive change in BMD with FES training, whereas 11 did not show any significant effect. All studies that demonstrated positive changes in BMD used training durations of at least 9 months, stimulated 3-5 hours per week, and measured bone sites that would have received loading based on the types of stimulation used. In contrast, all negative studies had one or a combination of the following elements: training intervention durations of less than 9 months

Rationale

Neuromuscular Electrical Stimulation

There is very low-level evidence (2 primary observational studies, nonrandomized) that performing lower limb NMES for 2.5-5 hours per week (in 3-5 sessions) for a minimum duration of 24 weeks can partially reverse bone mineral loss at the distal femur and proximal tibia.^{457,458} Risk of bias was generally low for these NMES studies (see Appendix E, Figure B6.11). There is moderate evidence that NMES with low adherence (<2.5 times per week) or short duration will not increase BMD.⁴⁵⁸

Functional Electrical Stimulation

There is moderate- to high-level evidence (controlled primary observational intervention studies) that bone sites that do not directly receive contractile forces during FES-induced muscle contractions will not show increased BMD.⁴⁵⁹⁻⁴⁶⁴

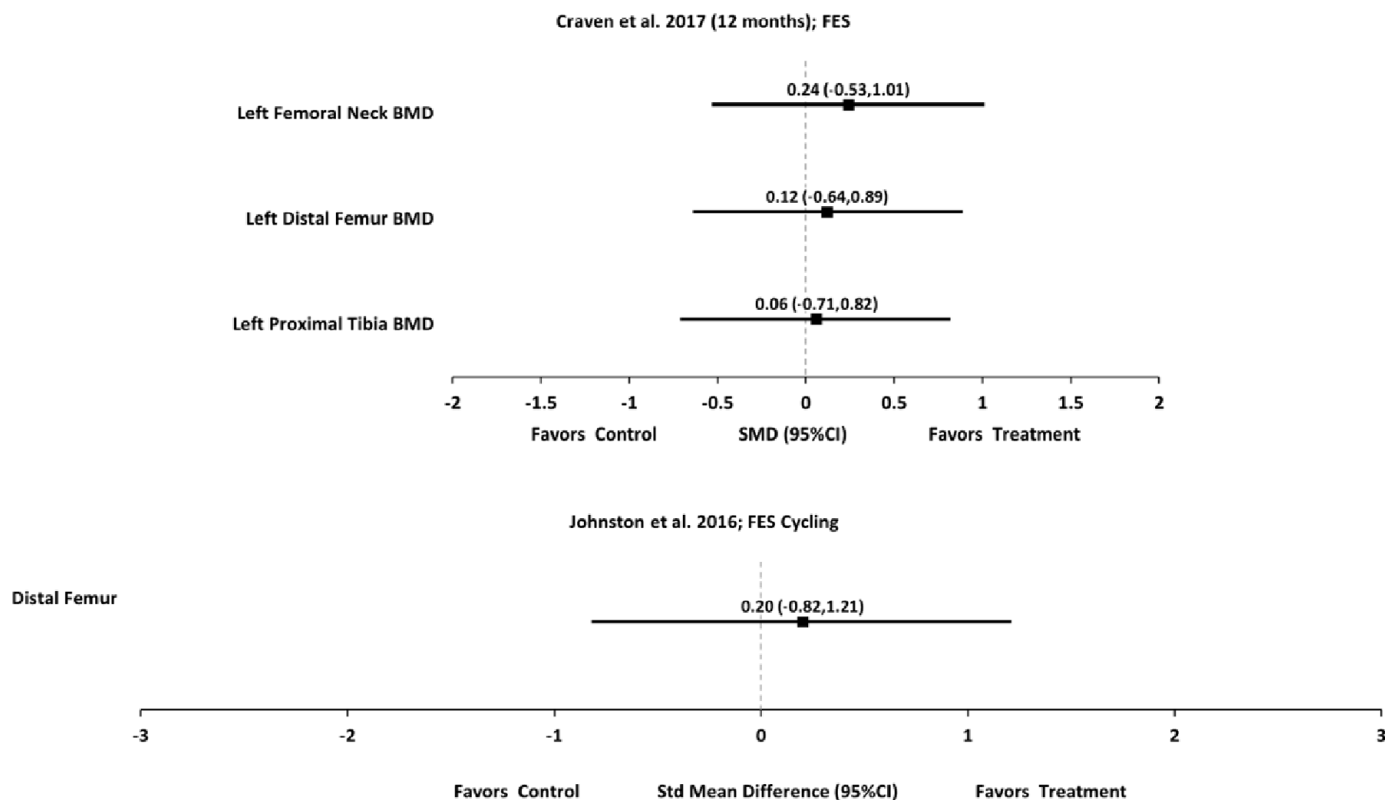
There is high-level evidence (controlled observational intervention studies) that increases in BMD will remain only while training is maintained.^{276,461}

There is high-level evidence (multiple controlled and uncontrolled primary observation intervention studies) that training intervention durations of <6 months are insufficient to allow bone changes to occur, as shown by an absence of significant changes in BMD.^{284,462,463,465-468} Related effect size diagrams for 2 of these studies are shown in Figure 6.1.

(7 studies), low weekly training volumes or low levels of loading (5 studies), or measured BMD at sites remote from muscles being stimulated (3 studies). In cases where either FES or NMES is stopped or reduced to once per week, improvements in BMD are not well maintained.^{276,471} Risk of bias varied for

RCTs (see Appendix E, Figure B6.12) and observational studies (see Appendix E, Figure B6.13) that examined the effect(s) of FES on BMD. Effect size diagrams are shown for the 2 studies for which there was sufficient detail to calculate effect size.

Figure 6.1. Effect size diagrams for 2 randomized controlled trials, 1 by Craven et al.⁴⁶⁶ and 1 by Johnston et al.,⁴⁷² in which functional electrical stimulation (FES) for a duration less than 9 months was insufficient to increase bone mineral density (BMD) in persons with chronic spinal cord injury. SMD, standardized mean difference; CI, confidence interval.



7.0 DRUG THERAPY

Preamble

This section addresses the use of prescribed medications for both the prevention and treatment of low bone mineral density (BMD) following spinal cord injury (SCI). Prevention is defined as intervention prior to the development of low BMD and increased fracture risk. In contrast, treatment is defined as an intervention in the context of established low BMD and increased fracture risk. Prescribed medications are often used for both prevention and treatment. The ultimate goal of therapy is to prevent near-term or future fractures.

Context

Bisphosphonates (BPs) are a class of antiresorptive compounds that are widely used in the treatment of postmenopausal, glucocorticoid-induced, and senile osteoporosis to augment BMD and/or reduce fracture risk.⁴⁷³ There are 2 subclasses of BP: (1) the less potent, more quickly metabolized, non-nitrogen-containing first-generation BPs (e.g., etidronate, clodronate, tiludronate) and (2) the more potent, less quickly metabolized, second- and third-generation nitrogen-containing BPs (e.g., alendronate, risedronate, pamidronate, ibandronate, and zoledronic acid [ZA]). Nitrogen-containing BPs promote osteoclast apoptosis, and the underlying mechanisms for apoptosis are

distinct from that of the non-nitrogen-containing BPs.⁴⁷⁴ A small number of randomized controlled trials (RCTs) have evaluated the efficacy of BP therapy for preventing a decline in hip and knee region bone density among individuals with acute SCI, who typically have normal bone density at injury onset.

In comparison to BPs, denosumab represents a novel class of antiresorptive therapy. Denosumab is a human monoclonal antibody with high affinity and specificity for binding the receptor activator of nuclear factor kappa-B ligand (RANKL). RANKL activates RANK, a surface receptor that facilitates the maturation of preosteoclasts into osteoclasts, promotes osteoclast activity, and maintains osteoclast viability. The binding of denosumab to RANKL inhibits its actions and the associated upregulation of osteoclast activity. Denosumab is a potent antiresorptive agent for treating different models of osteoporosis,^{475,476} more potent than BPs in postmenopausal women, and has been found to have greater efficacy in reducing nonvertebral fractures.⁴⁷⁷⁻⁴⁷⁹ A recent RCT evaluated the efficacy of denosumab for the prevention of bone loss in a cohort of individuals with subacute motor complete SCI.⁴⁸⁰

Evidence supporting the efficacy of nitrogen-containing BPs and denosumab in preventing the secondary loss of bone mass among individuals with acute and subacute SCI are reviewed below. Risk of bias (see Appendix E) and effect size diagrams are provided for each interventional trial for which the effect size could be calculated.

The implications for maintaining areal BMD (aBMD) or volumetric BMD (vBMD) of the total hip, femoral neck, distal femur (DF), and proximal tibia (PT) are also discussed. Available evidence includes open-label and RCTs of BPs. The number of RCTs that have evaluated BP therapy for the preservation or enhancement of BMD following SCI is small. To date, studies that have evaluated the efficacy of oral and intravenous (IV) BPs to attenuate bone loss after acute SCI include 6 trials with Level I and II evidence (generally characterized by small sample sizes). There is 1 trial with Level I evidence for denosumab.

Studies and trials that evaluated first-generation BPs were excluded from this review because (1) agents are no longer produced or available in North

America,⁴⁸¹ or (2) the primary study outcomes were bone histomorphometry,⁴⁸² biomarkers of bone formation and resorption without imaging,^{4,483} or photon absorptiometry (a dated technology),⁴⁸⁴ all of which were deemed to have limited relevance for current clinical practice. One study that enrolled a heterogeneous cohort of participants with acute and chronic SCI,⁵³ the majority being chronic (injury duration ≥ 1 year), is discussed under Recommendation 7.4 for treatment rather than prevention. Tables of the included and excluded studies considered in formulating our recommendations are provided in Appendix C (Tables 7A-7I).

Beyond BPs and denosumab, additional agents have been developed and recently introduced for the treatment of low BMD in the able-bodied population. Examples include romosozumab and abaloparatide. In the future, the number of therapeutic options will increase further. At the current time, however, there is no existing evidence to guide their use in individuals with SCI. A discussion of their use in the context of SCI is therefore beyond the scope of the current evidence-based practice guidelines. As a result, the appropriateness of their use for individuals with SCI is left to the discretion of treating clinicians. Finally, along with any prescribed therapy, a multimodal approach should be used that takes into account the confounding effects of rehabilitation, nutrition, hormones, and medical and family history on bone loss and fracture risk in individuals with SCI.

Safety Considerations

BPs are contraindicated in pregnancy and should be used with caution in premenopausal women who have the potential to become pregnant. There are common side effects and rare serious adverse reactions associated with BP therapy. Common side effects include gastroesophageal inflammation (oral BP), nephrotoxicity (with IV ZA), and atrial fibrillation. The requirement to remain upright for 30 minutes after administration and the potential for gastroesophageal inflammation should be taken into account when administering an oral BP (e.g., alendronate) in the context of acute SCI. Individuals experiencing gastroesophageal irritation can be switched to an IV BP. In the general population, the risk of nephrotoxicity or renal impairment related to the administration of IV ZA can be reduced by excluding patients with a creatinine clearance of <30 - 35 mL/min and by extending the

administration over a longer period. Acute febrile myalgic reactions have also been described with IV BPs, typically following the initial infusion. In trials for acute SCI, acute febrile myalgic reaction (fever) has been the most commonly reported adverse effect following the administration of IV ZA.⁴⁸⁵⁻⁴⁹⁰ In a recently published study by Oleson et al.,⁴⁸⁹ 7 of the 8 participants with moderate- to high-grade fever were in the ZA group. Furthermore, one participant in the ZA group experienced acute kidney injury 6 days after receiving the study drug (creatinine rise of 1.2 points from baseline). Creatinine levels returned to baseline following aggressive hydration and IV antibiotics 5 days after the diagnosis of acute kidney injury. The author attributed the higher prevalence of adverse reactions to the administration of ZA within 10-21 days of SCI, which is earlier than in any previous study that used ZA. There were no reports of atrial fibrillation, renal impairment, or gastrointestinal disturbances in the ZA trials.

Hypocalcemia has also been reported with BP administration, particularly in the setting of vitamin D deficiency or inadequate dietary calcium intake. Consequently, consideration can be given to checking serum calcium and 25-hydroxyvitamin D levels prior to initiation of BP therapy.

More serious and rare adverse reactions, such as osteonecrosis of the jaw (ONJ) and atypical femoral fracture, have been reported with long-term BP therapy. Patients with prior cancer and radiotherapy are at greatest risk for developing ONJ.^{491,492} The reported incidence of ONJ in patients receiving long-term BP administration for osteoporosis ranges from 1 per 10,000 to 1 per 100,000 patient-treatment years.⁴⁹³ **Prior to BP administration, clinicians are encouraged to examine the patient's oral cavity for exposed gums, broken or abscessed teeth, or gum disease.**

Atypical femoral fracture is characterized by a fracture at the subtrochanteric or femoral shaft with minimal trauma. This is typically preceded by thigh or groin pain, originating at the lateral cortex and extending through both cortices, with localized periosteal or endosteal cortical thickening.⁴⁹⁴ The reported incidence of atypical femoral fracture ranges from

1.8 per 100,000 per year after 2 years of BP exposure to 113 per 100,000 per year after 8 to 9.9 years of exposure,⁴⁹⁵ suggesting that the risk of atypical femoral fracture increases with duration of BP therapy. For primary osteoporosis, the benefit of reduced fracture risk from BP therapy is greater than the risk of developing either ONJ or an atypical femoral fracture.⁴⁷⁴ Notably, no definitive cases of ONJ or atypical femoral fracture have been reported following the prophylactic administration of BP during the acute phase of SCI.^{244,485-488,490,496,497}

Similar to BPs, denosumab is contraindicated in pregnancy and should be used with caution in premenopausal women who have the potential to become pregnant. There is also the potential for hypocalcemia when denosumab is administered to individuals with inadequate intake of calcium and/or vitamin D. A check of serum calcium levels is therefore recommended prior to administration of denosumab in individuals predisposed to hypocalcemia (e.g., hypoparathyroidism, thyroid surgery, parathyroid surgery, gut malabsorption). Dermatologic reactions such as dermatitis, eczema, and rashes have also been observed with denosumab administration. Similar to the case with BPs, ONJ and atypical femoral fracture have also been reported in individuals who are receiving denosumab. Consequently, clinicians should perform an oral inspection prior to initiating therapy with denosumab. Clinicians are reminded that fracture prevention was not a primary outcome of any trial reviewed in formulating recommendations 7.1 to 7.3.⁵⁷¹

The decision to prescribe medications for either the primary prevention or treatment of low BMD following SCI, or for fracture prevention, should use a shared decision-making process that takes into account patients' values, preferences, and comorbidities. In addition, it is important to consider the risk:benefit ratio for the individual. The determination of fracture risk is covered in detail in Section 1.0.

Concurrent Administration of Calcium and Vitamin D

The intake of calcium and vitamin D in reported studies varies considerably. This includes ad lib suggestions to consume the recommended daily allowance of calcium and vitamin D,^{485,487,488} vitamin D repletion when

absolute deficiency was diagnosed (<20 ng/mL) but dosage was not indicated,^{496,497} and prescribed calcium and vitamin D supplementation over the course of the study.^{485,490} In studies in which recommendations and supplementation were used, the 25-hydroxyvitamin D (25-(OH)D) absolute deficiency threshold (<20 ng/mL) was used to diagnose vitamin D deficiency.^{480,485-487,490} In the studies that prescribed calcium and vitamin D supplementation, 50,000 IU of vitamin D₂ was administered daily for no more than 6 days, followed by a maintenance dose of vitamin D₃ 800 IU daily.^{485,490} The concurrent administration of calcium and vitamin D may be important effect modifiers. As a result, calcium and vitamin D intake should be optimized and identified deficiencies corrected prior to prescribing medications to prevent or treat low BMD. Targets and strategies for achieving this are discussed in detail in Section 5.0.

Prevention

Recommendations

- 7.1

We recommend that clinicians and individuals with SCI use a shared decision-making process that accounts for patients’ values, preferences, and comorbidities when selecting therapy and avoiding adverse effects.
1C
- 7.2

We recommend, given the anticipated declines in hip and knee region areal bone mineral density (aBMD) during the first 12-18 months after injury, that a discussion of the risk-benefit ratio of currently available drug therapy occur with individuals with acute SCI who are anticipated to be primary wheelchair users.
1C
- 7.3

We recommend the administration of alendronate, zoledronic acid, or denosumab if, after discussion with the individual, there is a desire to prevent secondary bone mineral loss, taking into account the potential risk-benefit ratio.
1C

Clinical Consideration

- 7.1

There is insufficient evidence to recommend the prophylactic use of oral or IV BPs in individuals with acute SCI who will progress to ambulation (weight bearing) as their primary mode of mobility.
- 7.2

There is insufficient evidence to support the prophylactic administration of antiresorptives beyond the initial 18 months after injury. We suggest that treatment decisions at 18 months after injury be guided by determination of fracture risk, incorporating non-BMD risk factors and dual-energy X-ray absorptiometry (DXA) of the total hip, DF, and PT,²⁴ and reached in collaboration with the individual living with SCI.
- 7.3

Fracture prevention was not a primary outcome of any trial reviewed in formulating recommendations 7.1 to 7.3.⁴⁹⁸

Denosumab is relatively contraindicated in patients with significant lower extremity edema or lower extremity pressure sores because of the increased risk of cellulitis or clinically diagnosed erysipelas involving the lower extremities.⁴⁹⁹

Case reports in the non-SCI cancer population emphasize the need for regular monitoring of renal function during ZA treatment, with particular attention to patients with premorbid or known impairments in renal function.^{500,501}

Rationale

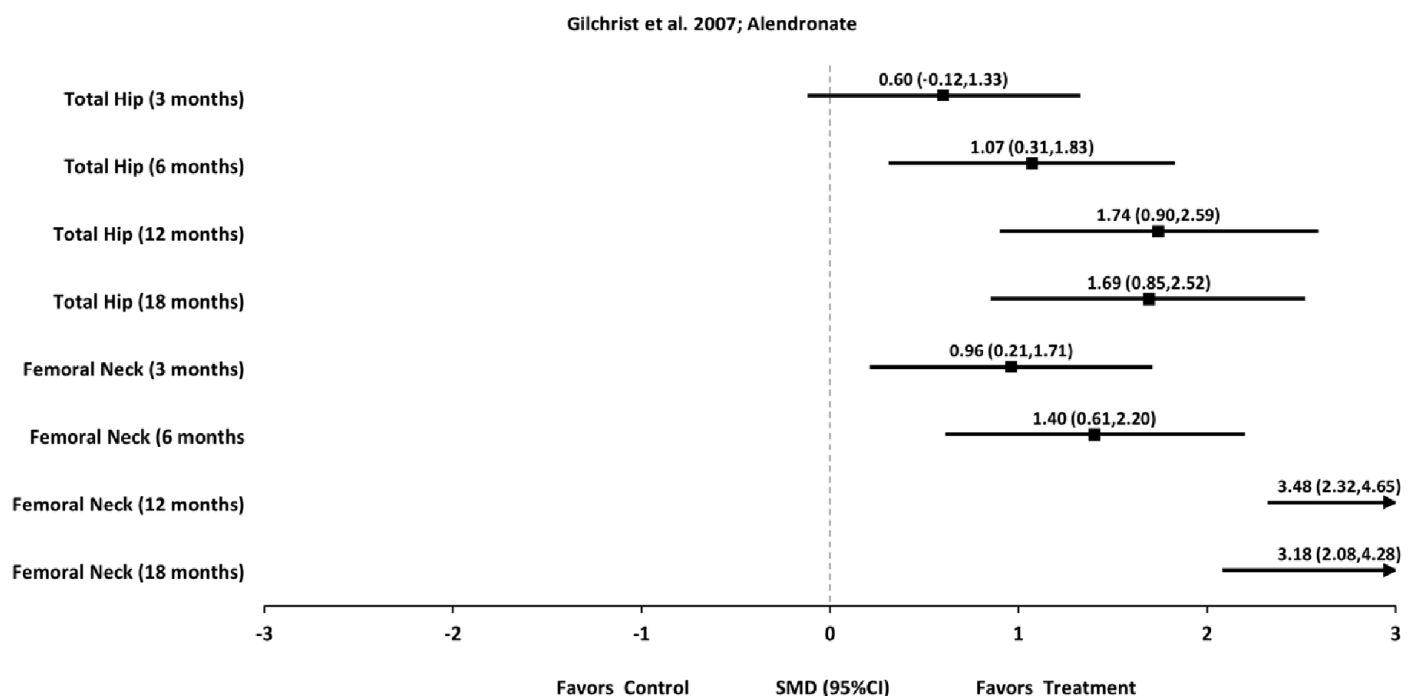
Alendronate

Alendronate is a nitrogen-containing amino BP that inhibits osteoclasts and accompanying bone resorption. Gilchrist et al.⁴⁹⁶ conducted an open-label RCT (Level 1C evidence) to determine the efficacy of oral alendronate 70 mg weekly for preserving aBMD when administered within 10 days of acute SCI and continued for 18 months. Twelve participants in the alendronate arm and 13 participants in the placebo arm completed the study. Six participants were

withdrawn because of either poor compliance (n=4) or lack of follow-up (n=2). Participants with serum (25-(OH)D) levels of <50 nmol/L received vitamin D supplementation. aBMD was measured for the whole body, femoral neck, trochanter, femoral shaft, total hip, and total legs. Compared with that in the control arm, aBMD was preserved in the alendronate arm 12 and 18 months after intervention. In particular, declines in

aBMD at 12 months after intervention were absent or reduced at the total hip (-3.3% vs. 20.9%, respectively) and femoral neck (+0.3% vs. -16.4%, respectively). Significant differences between the 2 study arms were still evident for total hip and femoral neck aBMD at 18 months. A risk of bias summary is provided in Appendix E, Figure B7.1, and the effect size diagram for Gilchrist et al.⁴⁹⁶ is shown in Figure 7.1.

Figure 7.1. Effect size diagram for a randomized control trial by Gilchrist et al.⁴⁹⁶ in which alendronate was used to prevent bone loss in a cohort of individuals with acute spinal cord injury. BMD, bone mineral density; SMD, standardized mean difference; CI, confidence interval.



Pamidronate

Pamidronate is a BP currently approved by the U.S. Federal Drug Administration for the treatment of hypercalcemia but not osteoporosis. Bauman et al.⁴⁸⁶ performed a small, double-blinded, placebo-controlled RCT that compared pamidronate (60 mg IV/100 mL; n=6) with placebo (normal saline; n=5). Study participants consisted of adult men and women with motor complete SCI who received an initial infusion within 90 days of injury, followed by repeat infusions at 1, 2, 3, 6, 9, and 12 months after initial infusion. All participants received a daily multivitamin that incorporated vitamin D. The primary outcome was change in aBMD of the DF and PT 12 and 24 months after treatment. IV pamidronate failed to prevent bone loss at the DF and PT at 12 and 24 months (Level 2B

evidence).

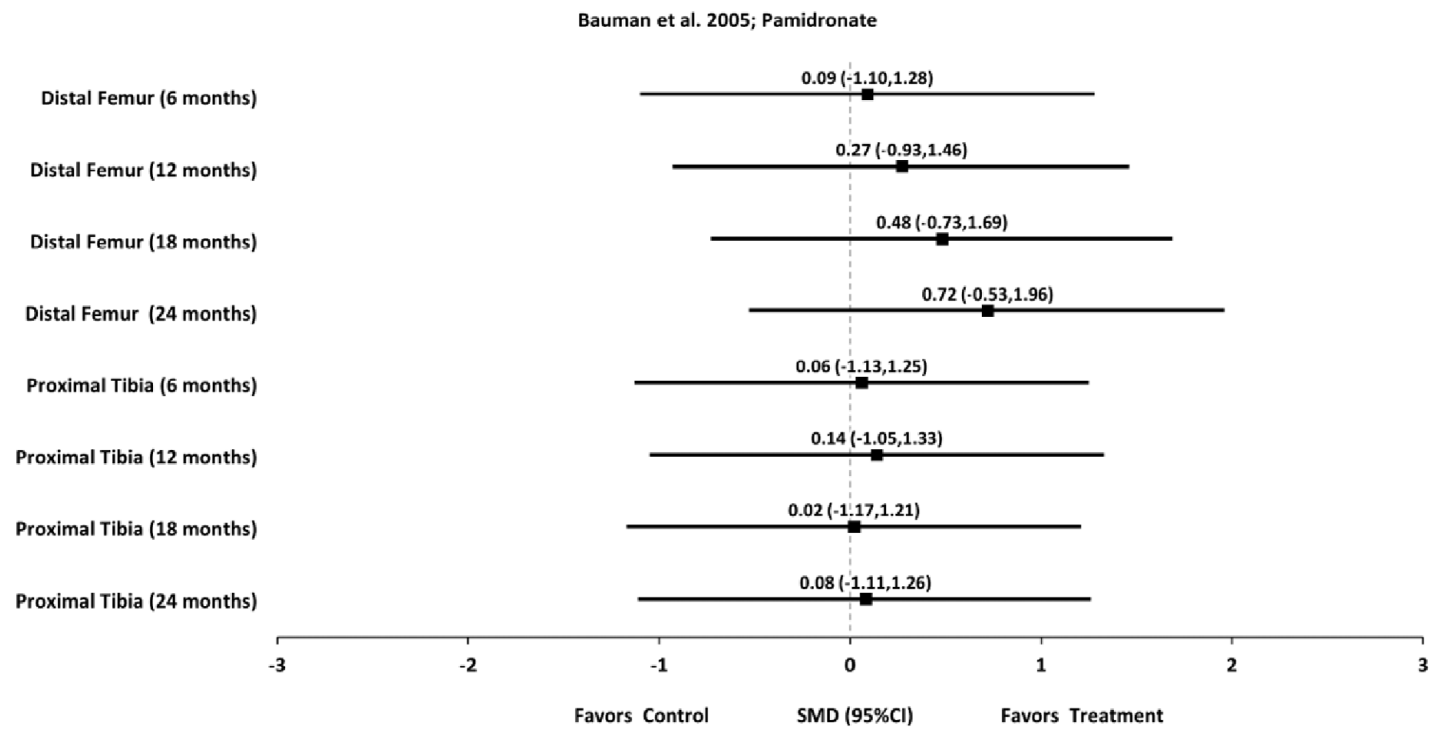
There is one trial with Level 1C evidence that suggests that IV pamidronate can attenuate bone loss if it is administered early after SCI. In a non-RCT, Nance and colleagues⁴⁸⁸ administered 6 treatments of IV pamidronate (30 mg, 7.5 mg/hour) at 4-week intervals to 14 adult male and female participants beginning within 6 weeks of injury. Ten controls received no treatment. Twelve months after the initial infusion, aBMD was preserved in the pamidronate arm at the hip, DF, and PT. There are, however, multiple confounders to consider when interpreting the pamidronate literature, including the heterogeneity of neurological impairments among trial participants (American Spinal Injury Association [ASIA] Impairment

Scale [AIS] grade A vs. grades B-D) and variability in the information provided regarding mobility (wheelchair or walking) and loading activities or therapies.

Risk of bias summaries for the pamidronate studies

are provided in Appendix E, Figures B7.2 and B7.3. The effect size diagrams corresponding to the RCT by Bauman et al.⁴⁸⁶ can be found in Figure 7.2.

Figure 7.2. Effect size diagram for a randomized controlled trial by Bauman et al.,⁴⁸⁶ in which pamidronate was used to prevent bone loss in a cohort of individuals with acute spinal cord injury. BMD, bone mineral density; SMD, standardized mean difference; CI, confidence interval.



Zoledronic Acid

There are 5 studies with Level 1 evidence addressing the efficacy of IV ZA administration for the preservation of BMD following acute SCI.^{244,485,487,489,490,497}

Schnitzer and colleagues⁴⁹⁷ evaluated the efficacy of IV ZA (5 mg/100 mL normal saline) infused over 30 minutes within 6 months of injury in a double-blinded, randomized, placebo-controlled trial. Study participants consisted of 12 adult males and females with motor complete and incomplete SCI (6 treated with ZA and 6 receiving placebo). The primary outcome was the group mean change in total hip aBMD from baseline to 6 months after drug administration. Secondary outcomes included group mean change in DF and PT aBMD. Compared with the ZA arm, the placebo arm lost a higher percentage of aBMD at the total hip, with no differences in aBMD observed at the DF and PT (Level 1C evidence).

Similarly, Shapiro et al.⁴⁹⁰ administered either 4 mg (n=4) or 5 mg (n=4) of IV ZA diluted in 50 mL of normal saline over 15 minutes, or alternatively placebo (n=9), to adult male and female participants with acute motor complete (AIS-A or AIS-B) traumatic SCI within 90 days of injury. Participants with low serum 25-(OH) D received oral supplementation. The primary outcome was group mean change in total hip and femoral neck aBMD 6 and 12 months after infusion. Compared with placebo, aBMD at the total hip was maintained at 6 months following the administration of ZA, but not at 12 months after infusion (Level 1C evidence).

In the most recent RCT that examined the efficacy of ZA to attenuate aBMD loss during the acute phase of SCI, Oleson et al.⁴⁸⁹ administered 5 mg IV ZA (n=10) or alternatively placebo (n=5), diluted in 50 mL normal saline over 2 hours (i.e., 2.5 mg/hour 2 hours), to adult male and female participants with sensory and motor complete (AIS grade A) traumatic SCI within 21 days of

injury. Participants with low serum 25-(OH)D received oral supplementation to raise their level above 13 ng/mL. The primary outcome was group mean change in aBMD at the total hip and subregions (intertrochanteric area and femoral neck), DF, and PT at 4 and 12 months after ZA infusion. Compared with those in the ZA arm, participants in the placebo arm experienced a greater decline in aBMD at the total hip 4 months (0.92% vs. -12.0%, respectively) and 12 months (-8.2% vs. -21.3%, respectively) after infusion. Furthermore, aBMD at the DF but not the PT was maintained at 4 months following the administration of ZA; however, this was not sustained at 12 months after infusion (Level 1C evidence).

The findings that ZA was effective at preserving aBMD at the total hip and subregions but not at the DF and PT 12 months after infusion is supported by all previous work using ZA, with the trial conducted by Bauman et al.⁴⁸⁵ being the most relevant for comparison. This is because both studies used the same custom region-of-interest methodology to capture aBMD of the DF and PT.

In a randomized, open-label study (n=14), Bubbear and colleagues⁴⁸⁷ also investigated the efficacy of IV ZA (4 mg/100 mL) infused within 90 days of injury to individuals with acute SCI. Seven participants were treated with drug, whereas 7 received standard care. The primary outcome was mean group change in aBMD at the total hip and femoral neck. Absolute aBMD of the total hip was higher in the treatment group 12 months after infusion; however, no significant difference was observed at the femoral neck (Level 1C evidence). In another non-randomized open-label study, Bauman and colleagues⁴⁸⁵ administered ZA 5 mg/100 mL over 30 minutes to 13 adult male and female individuals with acute motor complete SCI (AIS-A or AIS-B) within 90 days of injury. Six study participants received ZA, whereas 7 others did not. All participants received calcium carbonate 1,250 mg daily. In addition, those with a serum 25-(OH)D level

of <20 ng/mL received vitamin D 50,000 IU daily for 5 days followed by vitamin D 800 IU daily. The primary outcome was group mean change in DF and PT aBMD. Compared with the treatment arm, control participants experienced a greater decline in aBMD at the total hip at 6 months (-3.2% vs. -13.9%, respectively) and 12 months (-7.5% vs. -20.1%, respectively) after infusion. Surprisingly, in contrast to aBMD at the total hip, aBMD at the DF declined to a greater extent in the treatment arm than in the control arm at 12 months after treatment (-18.5% vs. -8.4%, respectively) (Level 2C evidence). The significant findings from Bauman et al. should be interpreted with caution, as the effect size diagram demonstrates a 95% confidence interval range at the femoral neck and total hip that favors treatment participants (Figure 7.6), a disparity between the different analyses that may be attributed to the extremely small sample size.

In the largest trial to date to assess the efficacy of ZA for the preservation of BMD following acute SCI, Goenka and colleagues²⁴⁴ infused IV ZA (5 mg IV/100 mL) in an open-label RCT to 60 adult men and women (intervention n=30; control n=30) with acute SCI (AIS grades A, B, and C) within 90 days of injury. Loss of aBMD was ameliorated at the total hip and femoral neck at 6 months and 12 months after infusion in individuals treated with ZA compared with that of controls (Level 1C evidence).

In summary, there is Level 1 evidence in 5 small trials that suggests that IV ZA 5 mg infusion given within 90 days of acute SCI can prevent or ameliorate aBMD loss in the lower extremities. Unfortunately, the trials by Bubbear et al.,⁴⁸⁷ Shapiro et al.,⁴⁹⁰ and Goenka et al.²⁴⁴ did not evaluate regional changes in DF and PT aBMD, the most common fracture sites following SCI. Risk of bias summaries are provided in Appendix E, Figures B7.4 and B7.5. Effect size diagrams for these 5 ZA interventions can be seen in Figures 7.3, 7.4, 7.5, 7.6, and 7.7.

Figure 7.3. Effect size diagram for a non-randomized open-label study by Bauman et al.⁴⁸⁵ in which zoledronic acid was used to prevent bone loss in a cohort of individuals with acute spinal cord injury. BMD, bone mineral density; SMD, standardized mean difference; CI, confidence interval.

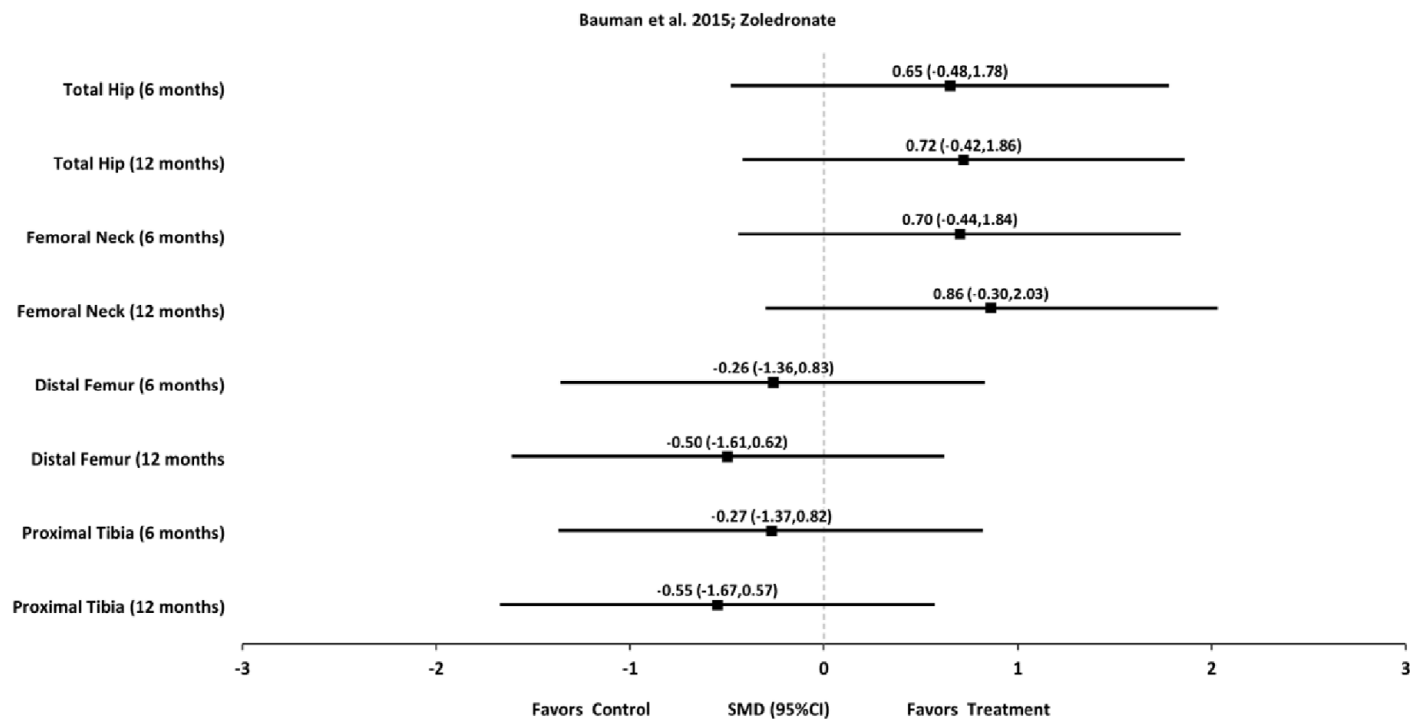


Figure 7.4. Effect size diagram for a randomized controlled trial by Bubbear et al.,⁴⁸⁷ in which zoledronic acid was used to prevent bone loss in a cohort of individuals with acute spinal cord injury. BMD, bone mineral density. BMD, bone mineral density; SMD, standardized mean difference; CI, confidence interval.

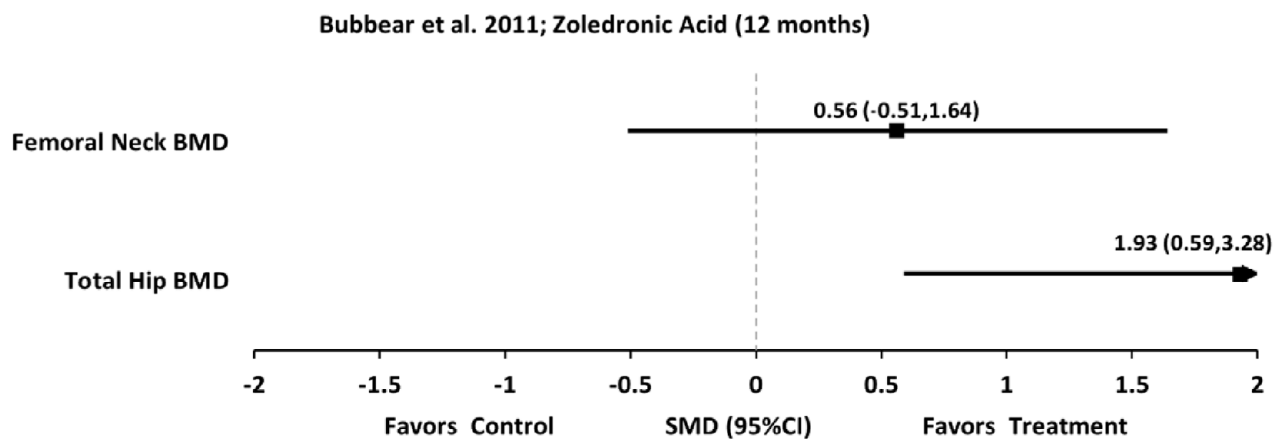


Figure 7.5. Effect size diagram for a randomized controlled trial by Oleson et al.,⁴⁸⁹ in which zoledronic acid was used to prevent bone loss in a cohort of individuals with acute spinal cord injury. BMD, bone mineral density; SMD, standardized mean difference; CI, confidence interval.

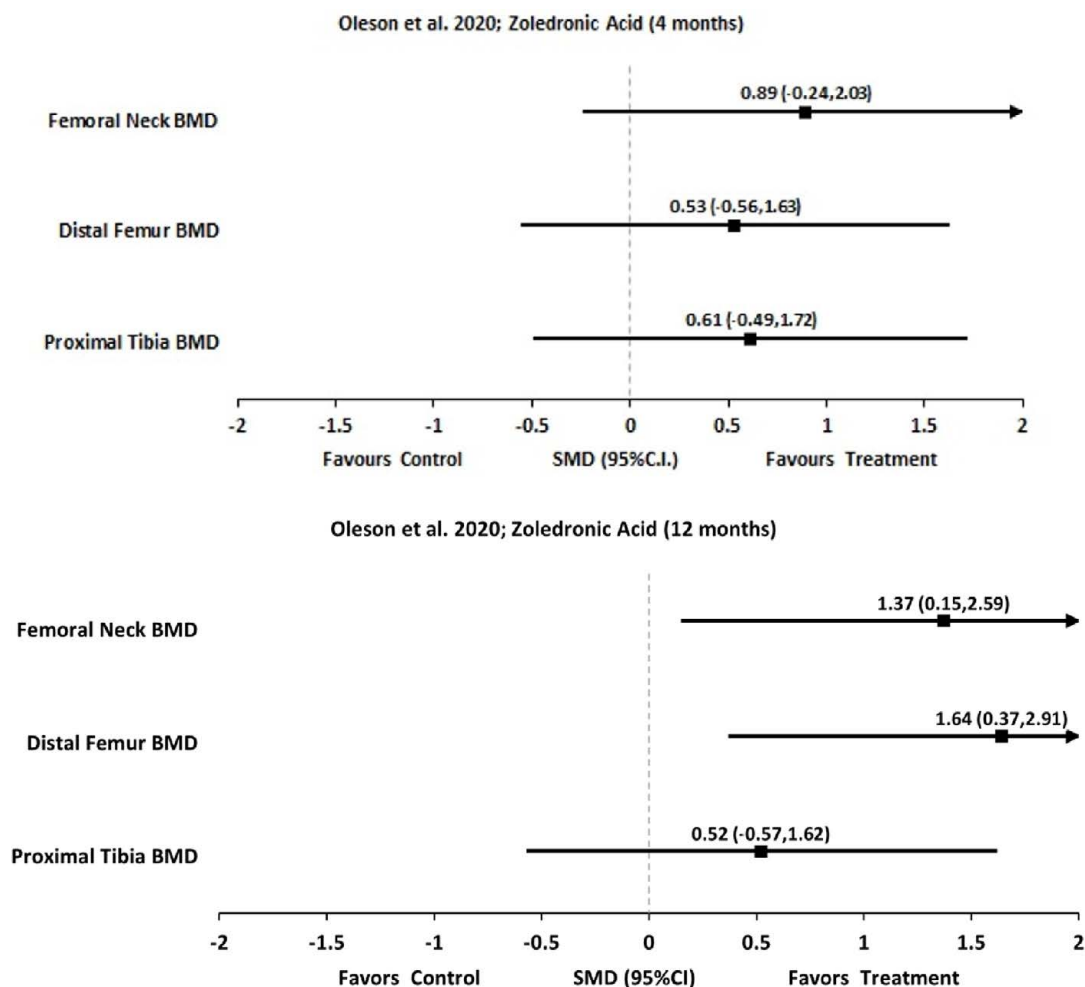


Figure 7.6. Effect size diagram for a randomized controlled trial by Schnitzer et al.,⁴⁹⁷ in which zoledronic acid was used to prevent bone loss in a cohort of individuals with acute spinal cord injury. BMD, bone mineral density; SMD, standardized mean difference; CI, confidence interval.

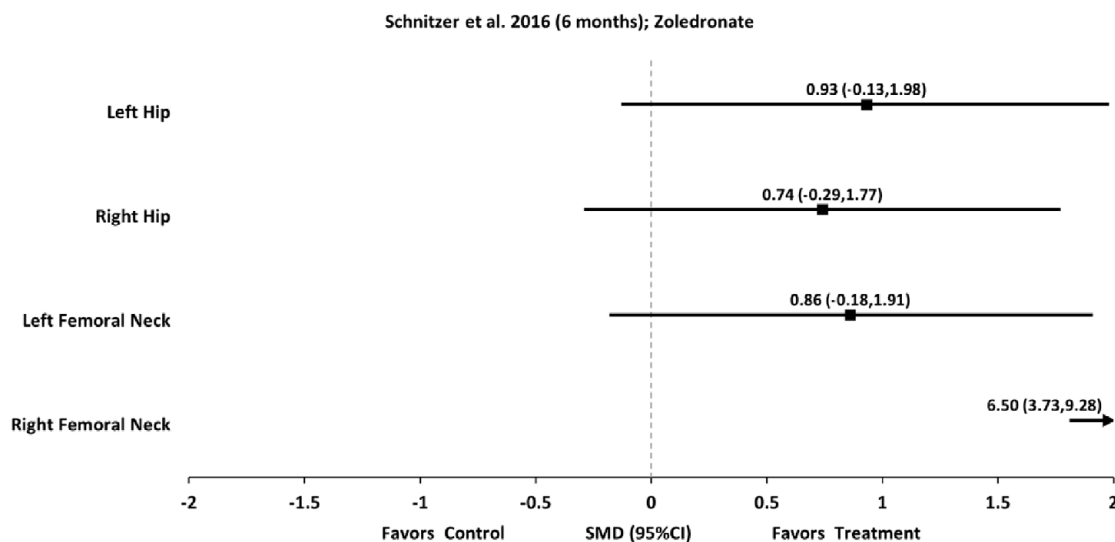
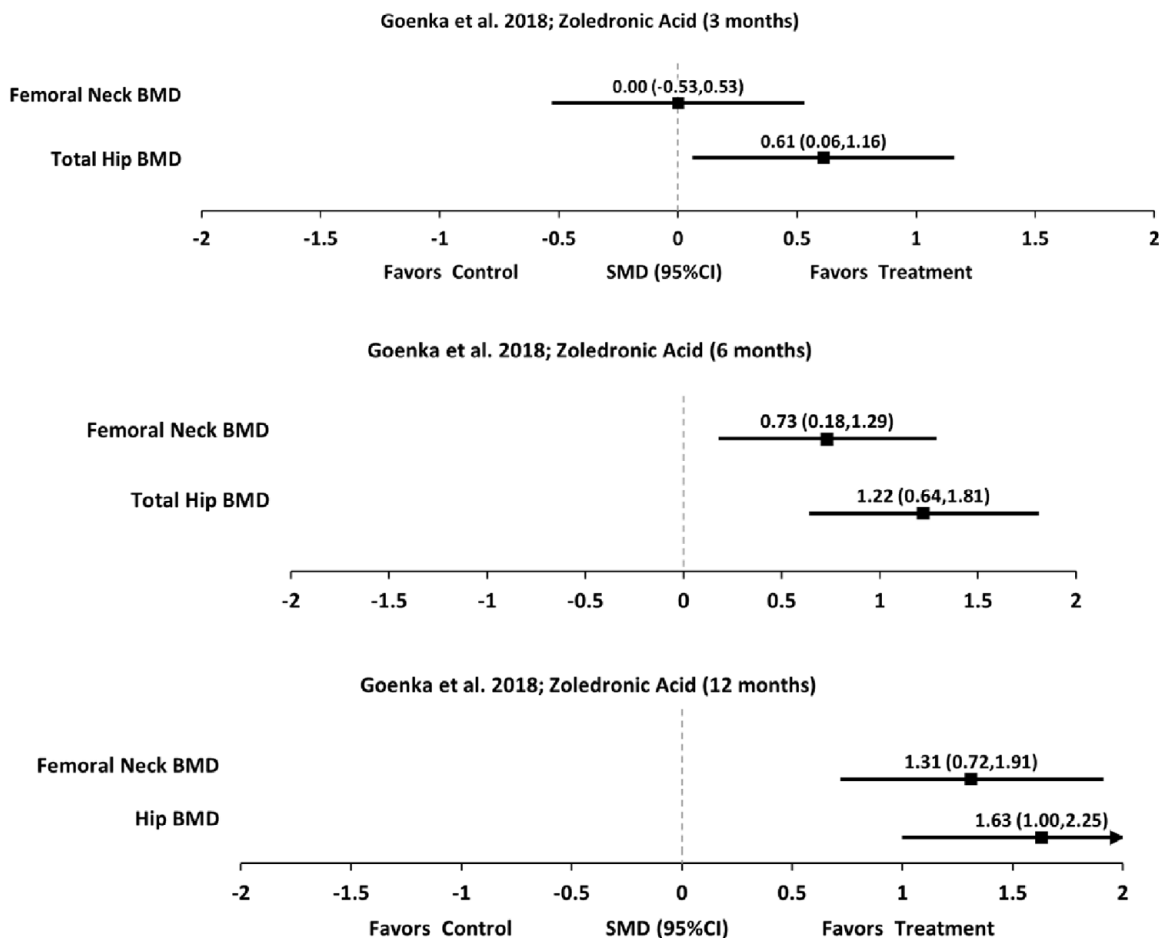


Figure 7.7. Effect size diagrams for a randomized controlled trial by Goenka et al.,²⁴⁴ in which zoledronic acid was used to prevent bone loss in a cohort of individuals with acute spinal cord injury. BMD, bone mineral density; SMD, standardized mean difference; CI, confidence interval.

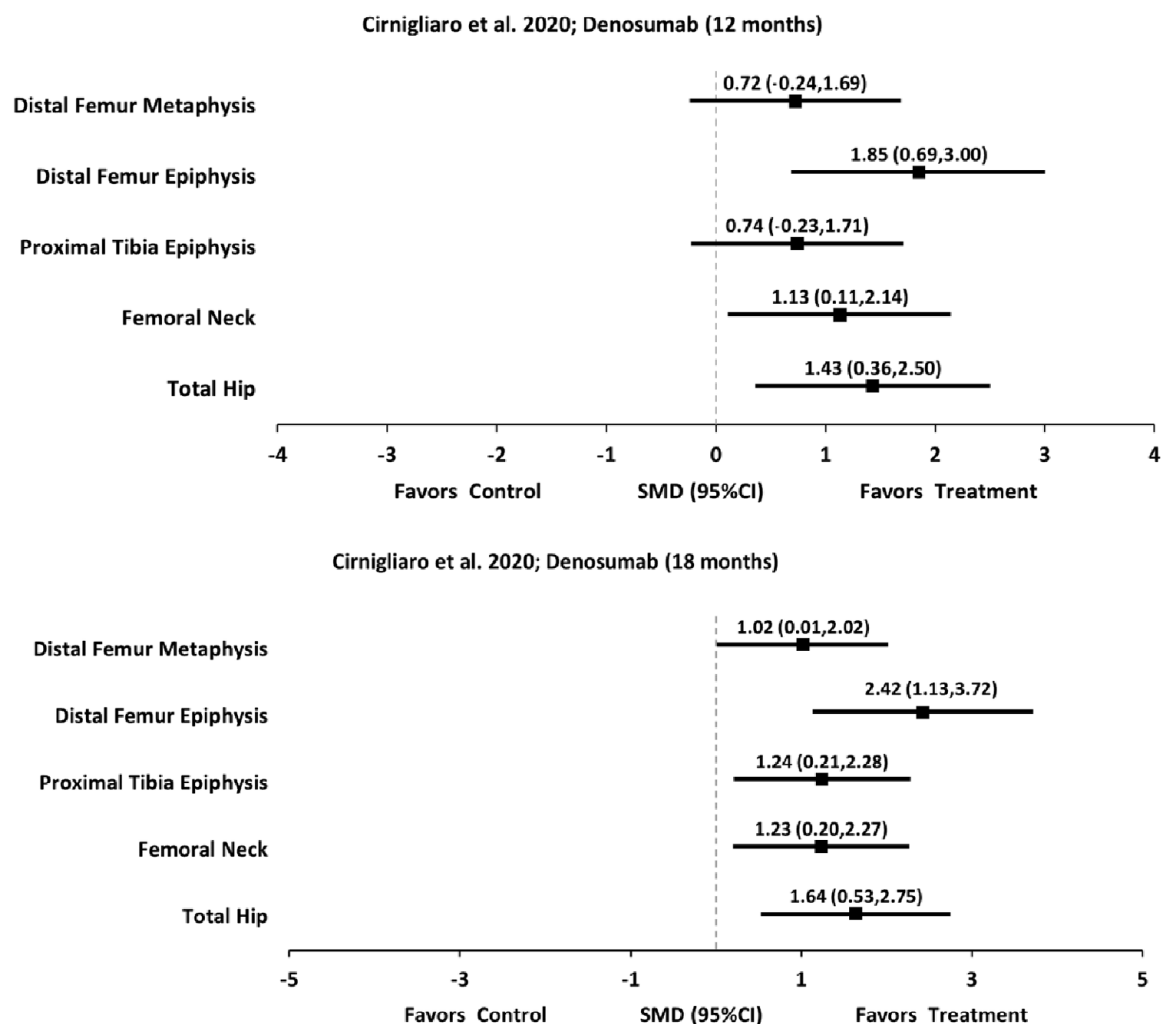


Denosumab

As described earlier, denosumab is a monoclonal antibody, which binds to and inhibits RANKL, a mediator of osteoclast formation and survival. It is therefore a potent antiresorptive. There is 1 study with Level 1C evidence that addresses the efficacy of denosumab administration for the preservation of BMD following subacute SCI. In an RCT by Cirnigliaro et al.,⁴⁸⁰ 26 male and female participants with acute motor complete (AIS grades A and B) SCI were randomized to receive either subcutaneous (SC) denosumab (60 mg) or placebo injections. Participants were within 90 days of injury. Injections were administered at baseline, and then repeated at 6- and 12-month intervals following the initial injection. The primary outcomes were aBMD at the distal femur metaphysis (DFM) and distal femur epiphysis (DFE), as measured by DXA at 18 months after treatment. Secondary outcomes included aBMD of the proximal tibia epiphysis (PTE), femoral neck, and total hip. From the 26 participants initially

enrolled, data from 18 (denosumab, n=10; placebo, n=8) were included in the final analysis. Peripheral quantitative computed tomography was analyzed as an exploratory outcome in a subsample of the cohort (denosumab, n=7; placebo, n=7). To exclude vitamin D deficiency, the authors measured levels of serum 25-(OH)D at baseline. Participants who had vitamin D levels of <20 ng/mL at baseline were administered oral vitamin D₃ 4,000 IU daily for 30 days followed by 2,000 IU daily for the remainder of the study. At the 18-month time point, aBMD was preserved in the denosumab arm at the DFE, DFM, PTE, femoral neck, and total hip, whereas the placebo group lost significant aBMD at all regions of interest, ranging from 17.2% (DFM) to 30.0% (DFE). In summary, denosumab administered early after SCI preserved aBMD at the knee and hip 18 months following initial administration. The risk of bias summary is provided in Appendix E, Figure B7.6, and effect size diagrams for the study by Cirnigliaro et al.⁴⁸⁰ is shown in Figure 7.8.

Figure 7.8. Effect size diagrams for a randomized controlled trial by Cirnigliaro et al.⁴⁸⁰ in which denosumab was used to prevent bone loss in a cohort of individuals with acute spinal cord injury. BMD, bone mineral density; SMD, standardized mean difference; CI, confidence interval.



Risk of Bias Trends

In accordance with the Cochrane risk of bias criteria, no RCT demonstrated low risk of bias for all criteria. The RCTs by Shapiro et al.,⁴⁹⁰ Goenka et al.,²⁴⁴ Oleson et al.,⁴⁸⁹ and Cirnigliaro et al.⁴⁸⁰ demonstrated a high risk of bias in 1 criterion: reporting bias in Shapiro et al. and Oleson et al., performance bias in Goenka et al., and attrition bias in Cirnigliaro et al. (Appendix E, Figures B7.5 and B7.6). The studies by Nance et al.⁴⁸⁸ and Schnitzer et al.⁴⁹⁷ demonstrated a high risk of bias in 2 criteria: non-biased and adequate methodology as well as statistical analysis of potential confounds in Nance et al., and group similarities at baseline and incomplete outcome data in Schnitzer et al. (Appendix E, Figures B7.3 and B7.5). The study by Bubbear et al.⁴⁸⁷ demonstrated a high risk of bias in greater than 2 criteria: selection bias, performance

bias, detection bias, reporting bias, and attrition bias (Appendix E, Figure B7.5). To reduce risk of bias and increase the generalizability of future BP intervention studies, we recommend that authors do the following:

- Provide detailed descriptions of randomization procedures.
- Standardize and describe the concurrent administration of calcium and vitamin D supplements.
- Select an appropriate control intervention.
- Design trials that evaluate fracture risk reduction, rather than maintenance of aBMD (a surrogate for future fracture risk reduction).
- Ensure that assessors are blinded to group allocation.

- Select anatomical regions that are susceptible to fracture as the primary outcomes.
- Ensure an appropriate trial duration.
- Conduct multicenter trials with an adequate sample size (n>100).

Treatment

Recommendations

- 7.4 We recommend that individuals with SCI, low bone mass, and moderate-to-high fracture risk be offered oral alendronate, intravenous zoledronic acid, or subcutaneous denosumab combined with adequate calcium and vitamin D3 (see Section 5.0) to treat low total hip, distal femur, or proximal tibia aBMD.

1B

Clinical Consideration

7.4

Calcium and vitamin D intake should be optimized when treating documented low BMD and/or sublesional osteoporosis. Appropriate targets and strategies are discussed in detail above (see Section 5.0).

Although multiple oral BPs are available, studies of them for SCI are largely restricted to alendronate. When selecting oral BP therapy, recommendation 7.4 needs to be balanced against the distinct properties, routes of administration, and theoretical clinical advantages of individual agents. As an example, risedronate is often administered monthly (150 mg), as opposed to daily or weekly. Delayed-release risedronate can be taken with food and has been marketed for improved convenience, adherence, and tolerance.

Consideration can be given to administering IV ZA (BP) to individuals with SCI in whom treatment is indicated but oral BPs are contraindicated or who fail to respond to oral BPs.

Consideration can be given to administering SC denosumab to individuals with SCI who fail to tolerate or respond to oral or IV BPs at sites that have the potential to be affected by the FES and NMES intervention and not at a remote site.

Rationale

Multiple variables distinguish the treatment of established low BMD following SCI (chronic phase) from the pharmacological prophylaxis of anticipated declines in BMD following acute SCI. During the first 2 years after SCI, there are well-documented precipitous declines in trabecular BMD,⁵⁰²⁻⁵⁰⁵ after which the decline in BMD persists, but to a far lesser degree over the remaining lifespan of the individual.^{59,132} This later decline in BMD occurs primarily at the cortical region with concurrent changes to bone geometry and the trabecular architecture, resulting in diminished bone strength and an increased risk of fragility fracture.⁵⁰⁶⁻⁵⁰⁸ As a result, primary outcomes of pharmacological interventions during the chronic phase of SCI should ideally measure markers of bone strength in addition to surrogate measures such as BMD.

Decisions to treat low BMD following SCI should be based on the risk of fracture as the primary complication of low hip, DF, or PT BMD. The determination of fracture risk and the accompanying limitations of risk quantification are discussed in Sections 1.0 and 3.0. Interventions to treat low BMD in individuals with SCI should be initiated for individuals with a moderate-to-high fracture risk. Historically, large cohort sizes have been required to demonstrate fracture reduction in clinical trials that address low bone mass and osteoporosis in the general population.

To date, no clinical trials of individuals with SCI have demonstrated a reduction in fracture incidence. This is in part attributable to the challenges of performing large-scale SCI trials. The barriers related to participant identification, recruitment, and participation are formidable (e.g., low incidence and prevalence, medical stability, restrictive inclusion/exclusion criteria, availability of medical and social supports, transportation). The likelihood of completing large-scale clinical trials for low BMD and sublesional osteoporosis following SCI is therefore diminished.⁵⁰⁹

The current evidence base for the treatment of documented low hip, DF, or PT BMD and presumed moderate-to-high fracture risk in individuals with SCI comprises small clinical trials and case series. Risk of bias and effect size diagrams for each intervention trial for which the effect size could be calculated are shown

throughout this review. In lieu of directly determining fracture reduction, these studies used surrogate markers for fracture risk reduction, such as changes in regional BMD (e.g., aBMD). As a result, the primary outcomes used to appraise the existing evidence were BMD at the hip (total hip, intertrochanteric region) and knee (DF, PT) regions, the rationale being that these are the anatomical sites where the incidence of fracture is highest.

Pharmaceutical options that have been studied for the treatment of low BMD in individuals with SCI include the following: oral and IV BPs, SC denosumab, and SC recombinant parathyroid hormone (PTH; teriparatide). BPs and denosumab are antiresorptive agents that inhibit osteoclasts. Teriparatide is an anabolic agent and enhances osteoblastic activity. The accompanying safety considerations for BPs and denosumab are described in detail in the preceding section, which addresses the primary prevention of low BMD following SCI (see also Safety Considerations later in this section).

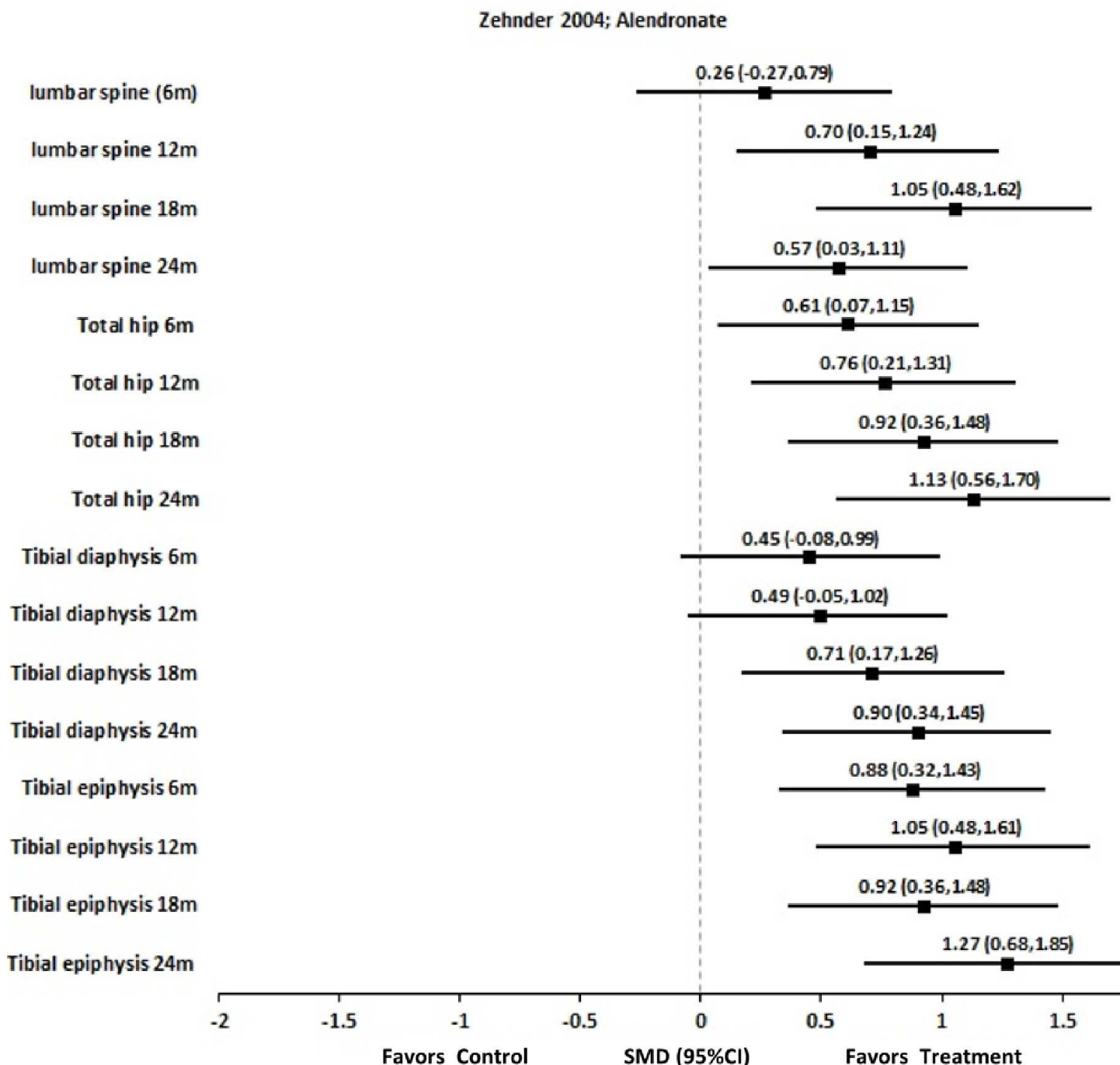
The primary concern related to the use of teriparatide is an observed increase in the incidence of osteosarcoma in preclinical studies of rodents.⁵¹⁰ The dose of teriparatide and the length of administration in the rodent studies was higher and longer, respectively, than the Federal Drug Administration-recommended parameters for treatment of osteoporosis. A recent 15-year post-marketing surveillance study found that the incidence of osteosarcoma was no different than what would be expected based on the background incidence rate of osteosarcoma.⁵¹¹ Relative contraindications include unexplained elevations of alkaline phosphatase, prior external beam or implant radiation therapy involving the skeleton, and a history of bone metastases or skeletal malignancies. Additional contraindications include other metabolic bone diseases (e.g., hyperparathyroidism, Paget's disease of the bone), pregnancy, and the absence of contraception in women of childbearing potential.

The evidence supporting the use of specific pharmaceutical agents for the treatment of documented low hip, DF, or PT BMD and/or sublesional osteoporosis following chronic SCI is discussed in the following subsections. Sublesional osteoporosis is a disease process that is characterized by excessive bone resorption and regional declines in BMD of the hip and knee regions early after traumatic SCI, which reduces bone quantity and quality, resulting in an increased propensity for lower extremity fragility fractures in the affected individual. It is important to acknowledge that although the existing evidence for individual agents is presented below, future studies are needed to establish the comparative efficacy of different pharmaceutical options.

Alendronate

In an RCT (n=55; 29 intervention, 26 control), Zehnder and colleagues⁵³ assessed the efficacy of oral alendronate for individuals with motor complete SCI. Participants in the intervention arm received oral alendronate 10 mg daily for 24 months. Both study arms received oral calcium supplements 500 mg daily. Participation was limited to men, and the participants had predominantly chronic injuries. Injury duration exceeded 6 months for 47 of 55 participants (25 intervention, 22 control), with a median post-injury duration of 9.8 years (range 0.1-27.2 years) in the intervention arm and 7.6 years (range 0.2-29.5) in the control arm. Twenty-nine participants in the intervention arm and 26 participants in the control arm completed study participation (injury duration for 4 participants was less than 6 months). The primary study endpoint was aBMD of the tibial epiphysis, and secondary endpoints included aBMD at the tibial diaphysis, ultradistal radius, radial shaft, total hip, and lumbar spine. Markers of bone resorption and bone formation were also measured. The intervention arm maintained aBMD at the tibial epiphysis, tibial diaphysis, and total hip, whereas aBMD declined in the control arm at the corresponding sites. All intergroup differences were significant (see effect size diagram, Figure 7.9).

Figure 7.9. Effect size diagram of a randomized controlled trial by Zehnder et al.⁵³ pertaining to alendronate. BMD, bone mineral density; SMD, standardized mean difference; CI, confidence interval.



Moran de Brito and colleagues³⁸¹ completed an RCT (n=19; 10 intervention, 9 control) to assess the efficacy of oral alendronate to treat low BMD in individuals with chronic SCI. Participants were classified as AIS grade A, B, or C. Participants in the intervention arm received oral alendronate 10 mg daily for 6 months. Both the intervention and control arms received oral calcium supplementation (500 mg twice daily). Mean time since injury was 38.7 months (range 22.8-77.5 months)

in the control arm and 61.0 months (range 13.1-255.7 months) in the intervention arm. Nine individuals in the intervention arm and 8 individuals in the control arm completed the trial and their data were analyzed. The primary outcome was whole-body aBMD (DXA) with regional sub analysis of the upper extremity, lower extremity, and trunk. Compared with primary analysis of designated anatomical regions (e.g., DF, PT), regional sub analysis of whole-body DXA lacks validity

for the determination of fracture risk. This is because of limitations in DXA resolution and unacceptable variability. A decision was therefore made to exclude this study from consideration when recommendations were formulated. Additional methodological limitations included the relatively small cohort sizes and the short study duration, given the nature of bone metabolism (Level 1C evidence).

Recently Haider and colleagues⁵¹² completed an open-label clinical trial of oral alendronate following teriparatide therapy in individuals with chronic SCI and low BMD. Participants (n=17) were > 1 year after injury, were non-ambulatory, and had participated in a prior randomized controlled trial in which they received 1-2 years of therapy with teriparatide. Intervention consisted of oral alendronate 70 mg weekly for 12 months combined with vitamin D₃ daily (cholecalciferol) 1,000 IU and calcium carbonate 1,000 mg daily. Outcomes included DXA (aBMD spine, hip), computed tomography (CT: DF, PT), serum markers of bone turnover, and calculated metrics of bone strength measured at baseline, 6 months, and 12 months. At 12 months, aBMD was maintained at the total hip and femoral neck and was increased at the spine. Twelve-month CT results were mixed with increased cortical bone mineral content at the DFE, DFM, distal femur diaphysis (DFD), and PTE. Cortical bone volume increased at the DFE, DFM, and PTE. Declines, however, were noted in cortical bone volume at the DFD and the proximal tibia metaphysis (PTM) and proximal tibia diaphysis. Serum markers were consistent with reduced turnover (Level 2C evidence).

Risk of Bias

In reference to Appendix E, Figure B7.7, although most participants in the trial by Zehnder and colleagues⁵³ had chronic SCI (median injury duration 7.6 years for the control arm and 9.8 years for the intervention arms), a minority of them had acute SCI (<12 months of injury duration). Additional sources of bias for the Zehnder et al.⁵³ trial included lack of blinding and selective reporting. The potential for bias was unclear for many aspects of the Moran De Brito et al.³⁸¹ trial, including selection bias, performance bias, detection bias, reporting bias, attribution bias, and analysis according to randomization. The open-label trial of Haider et al.⁵¹² lacked a control arm.

Denosumab

In an open-label uncontrolled trial (n=14), Gifre and colleagues⁵¹³ assessed the efficacy of denosumab for increasing BMD in individuals with SCI and densitometry-established osteoporosis at baseline. Participants had a mean injury duration of 15±4 months and received denosumab (60 mg/mL) at 6-month intervals for 12 months. Thirteen of 14 participants had motor complete injuries and 1 individual was graded as AIS-C impairment. Study endpoints included markers for bone turnover, as well as aBMD for the total hip and femoral neck. Compared with baseline, 12-month BMD was significantly increased at all studied sites. Markers for bone turnover were also decreased (Level 2C evidence).

Risk of Bias

The lone available study that assessed the efficacy of denosumab for treating sublesional osteoporosis following SCI is strengthened by the internal consistency among the reported study outcomes; however, there is a risk of selection bias because of the lack of randomization (control arm) and the accompanying potential for unidentified confounders. In addition, BMD outcomes were not assessed at common fracture sites in individuals with SCI, potentially limiting the generalizability of the findings (see Appendix E, Figure B7.8).

Teriparatide

Teriparatide is a 34-amino acid peptide that represents the N-terminal bioactive portion of human PTH. PTH receptors are present on both osteoclasts and osteoblasts. Teriparatide is anabolic when administered daily to postmenopausal women and older men. In a pilot study, Gordon and colleagues⁵¹⁴ investigated the impact of gait training and teriparatide on BMD and bone architecture in nonambulatory individuals with chronic SCI. Twelve participants were administered SC teriparatide 20 mcg/day while undergoing robotic-assisted stepping 3 times a week (targeted progression to 40 minutes per session with <50% weight support) for 6 months, followed by 6 months of teriparatide alone. All study participants received calcium 1,000 mg/day and vitamin D 1,000 IU/day. Study endpoints included aBMD (spine, total hip, femoral neck), magnetic resonance imaging to assess bone microarchitecture at the distal tibia, and serum

markers of bone turnover. At 12 months, there were no significant changes in aBMD or magnetic resonance imaging (Level 2C evidence).

Edwards and colleagues²⁶⁷ studied the efficacy of teriparatide and vibration for increasing BMD in nonambulatory individuals with complete or incomplete chronic SCI (>1 year duration). The RCT (n=61) assigned participants to 3 treatment arms: SC teriparatide 20 mcg/day plus sham vibration 10 min/day (n=20), placebo plus vibration 10 min/day (n=20), or SC teriparatide 20 mcg/day plus vibration 10 min/day (n=21). The study duration was 12 months and the endpoints included aBMD (spine, total hip, femoral neck, forearm, whole body, DF, PT), CT imaging of the DF and PT (vBMD, bone mineral content, bone volume), and markers of bone turnover. All participants received calcium carbonate 1,000 mg and vitamin D (cholecalciferol) 1,000 IU daily. Individuals who completed the 12-month study were given the option of participating in an open-label extension (n=25) in which all participants received teriparatide 20 mcg/day for an additional 12 months and had the optional use of vibration for 10 min/day. At 12 months, spine aBMD was increased for the teriparatide alone and teriparatide-vibration arms, whereas vibration alone was unchanged. At 24 months, spine aBMD was increased in all study arms, but was greater for individuals who received teriparatide in the RCT. Hip aBMD was also increased at 24 months in the initial teriparatide arms. For the teriparatide arms, there was no observed treatment effect for aBMD at the knee. There was no observed therapeutic effect attributable to vibration (Level 1C evidence).

Risk of Bias

The study by Gordon et al.⁵¹⁴ is hampered by the potential for selection bias because of the lack of randomization and the absence of a control group (see Appendix E, Figure B7.9). The study by Edwards et al.⁵¹⁵ demonstrates a low risk of bias in all categories (see Appendix E, Figure B7.10).

Zoledronic Acid

ZA is a potent IV BP that, in contrast to oral BPs, is administered once a year. Morse and colleagues²⁶⁸ conducted an RCT that compared functional electrical stimulation (FES)-assisted rowing alone with FES-assisted rowing combined with ZA in nonambulatory

individuals with chronic SCI (>18 months' duration). Twenty participants were randomized to combination therapy (10 analyzed) and 18 to FES rowing alone (10 analyzed). Training goals for FES were 30 minutes, 3 days a week, with an intensity of 75%-85% of peak heart rate. Study duration was 12 months and individuals in the ZA arm received 1 dose (5 mg/100 mL infused over 15 minutes). All participants received calcium 1,500 mg/day and vitamin D 1,000 IU/day. Volumetric CT scans of the DFM and PTM were performed to determine the following bone geometric properties: cortical thickness index (CTI), cortical compressive strength index, buckling ratio (BR), and bending strength index. Additional study endpoints included the cortical bone volume, cortical BMD, and cortical bone mineral content. The determination of change in BMD at the DF and PT (measured by DXA) was planned but abandoned because of the withdrawal of the study site responsible for this analysis. At 12 months after intervention, cortical bone volume, CTI, and BR were greater in the FES-assisted rowing + ZA arm compared with the FES rowing arm at both the DFM and the PTM. Findings suggested that ZA mitigated BMD loss. There was also a significant association between total rowing work and BR at the PT (Level 1C evidence).

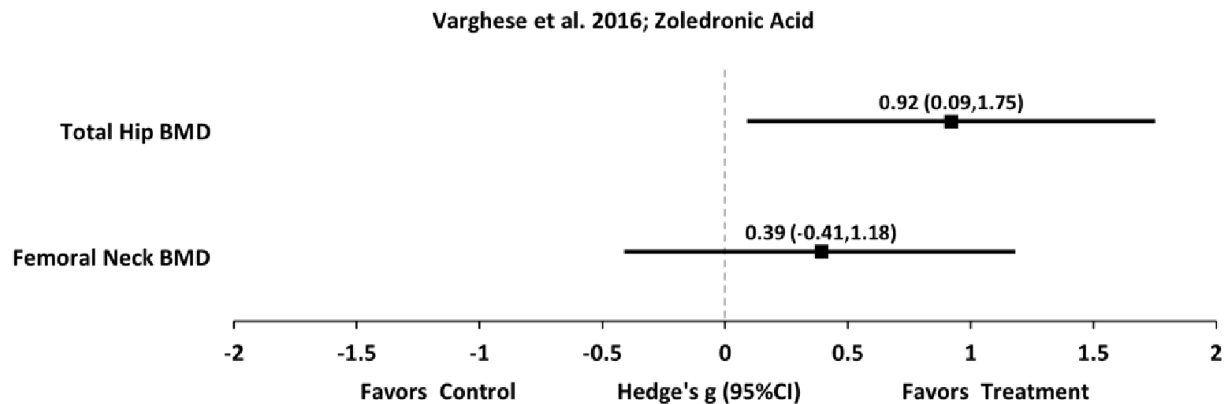
Varghese and colleagues²⁵⁴ assessed the efficacy of ZA for osteoporosis in individuals with chronic SCI (defined as injury duration >1 year) in a double-blind, randomized, placebo-controlled trial (n=28; ZA n=13, placebo n=15). Participants in the intervention arm received a single dose of IV ZA (4 mg/100 mL) infused over 20 minutes, and the placebo group received 100 mL normal saline. Study endpoints included aBMD of the total hip, femoral neck, total forearm, and distal third of the radius at 12 months. BMD of the forearm increased in both study arms. At 1 year, total hip aBMD declined significantly in the placebo group but not in the ZA study arm. At the same time point, femoral neck aBMD declined in both arms; however, the magnitude was greater in the placebo group. Compared with baseline values, aBMD of the distal radius increased in both study arms (see Figure 7.10). Outcomes were not assessed at common fractures sites (DF, PT) for individuals with chronic SCI (Level 1C evidence).

Risk of Bias

Significant sources of bias in the study by Morse and colleagues²⁶⁸ include the lost to follow-up rate and the incompleteness of available data for planned study outcomes (e.g., DXA). The trial of Varghese and

colleagues²⁵⁴ did not assess outcomes for common fracture sites in individuals with chronic SCI (see Appendix E, Figure B7.11), but overall was felt to have a low risk of bias.

Figure 7.10. Effect size diagram of a randomized controlled trial by Varghese and colleagues,²⁵⁴ assessing zoledronic acid. BMD, bone mineral density; SMD, standardized mean difference; CI, confidence interval.



Monitoring and Cessation of Ineffective Therapy

The optimal duration of osteoporosis therapy is not known. Placing a patient on therapy requires the physician to routinely assess treatment effectiveness and the presence or absence of side effects, as well as to have a low threshold for stopping ineffective therapy or therapy causing significant persisting side effects. Recommendations

- 7.5 We recommend that clinicians use the least significant change (LSC) to assess true biological change over time, defined as bone gain or bone loss that exceeds the LSC.
1A

Clinical Consideration
7.5
LSC is specific to the diagnostic tool used and its accompanying precision (sections 3.0 and 4.0).

- 7.6 We suggest that clinicians reassess (stop, continue, or change) osteoporosis therapies if significant bone loss occurs for 2 consecutive years despite good adherence.
2C

- 7.7 We suggest that clinicians reassess (stop, continue, or change) osteoporosis therapies if a long bone fragility fracture occurs in an individual with SCI who has been adherent to therapy for more than 1 year.
1D
- 7.8 One may consider initiating a drug holiday for individuals with moderate fracture risk following 5 years of consecutive treatment with oral bisphosphonate therapy or 3 years of intravenous bisphosphonate therapy.
2D

Clinical Consideration
7.8
Consider resuming therapy when a fracture occurs, hip or knee region BMD declines below the LSC, bone turnover markers rise to pretreatment values, or the patient meets the initial treatment criteria.⁵¹⁶

- 7.9 One may consider, for individuals with high and very high fracture risk or prior fracture, a treatment duration of 7-10 years for oral bisphosphonates or 6 annual doses of intravenous zoledronic acid.
2D

- 7.10 One may consider trialing an alternative intervention if side effects or poor adherence preclude continued therapy.

2D

Clinical Consideration

7.10

In the context of oral BP therapy, consideration can be given to changing the formulation (e.g., delayed release) or dosing interval (e.g., monthly). In addition, consideration can be given to alternatives to oral medications, such as IV ZA or SC denosumab, both of which are not dependent on absorption through the gastrointestinal tract.

In the context of anabolic therapy, clinicians should consider monitoring serum ionized calcium and creatinine levels closely because of the risk of developing hypercalcemia.

In the context of stopping therapy with denosumab, subsequent therapy with a BP is recommended because of the risk of vertebral fracture with sudden cessation of denosumab.

In the context of choosing an antiresorptive agent to prevent bone loss after acute SCI, whenever possible, an agent should be chosen that has evidence for preventing demineralization at the hip and knee regions.

Rationale

To date no intervention study has evaluated the efficacy of any intervention for reducing fracture risk. Most studies use an increase in BMD as a presumed surrogate for fracture risk reduction. In a recent study from the U.S. Veteran's Health Administration, Carbone and colleagues⁵¹⁷ used a matched nested case control design to evaluate the association between long-term BP therapy and incident fractures among male individuals with traumatic SCI. Routine prescription renewal was used as a surrogate for therapy adherence (cases). Controls were male veterans without access to osteoporosis medications during the study period. Among the cohort of 7,989 veterans, 267 received a BP prescription, 157 were adherent for 1 year, 65 for 2 years, 42 for 3 years, and 28 for 4 years. There was no significant association between long-term

use of BP therapy and lower extremity fractures at 2 years (hazard ratio [HR] 0.97, 95% confidence interval [CI] 0.25-3.75), 3 years (HR 1.17, 95% CI 0.26-5.35), or 4 years (HR 1.02, 95% CI 0.13-7.89).⁵¹⁷ These data suggest that the long-term use of BP therapy was not associated with fracture prevalence among males with SCI. The observed poor adherence in this study, combined with previously reported gastrointestinal side effects⁵¹⁸ as the primary reason for nonadherence, are important observations. Clinicians need to determine whether therapy is ineffective or, alternatively, the individual has been nonadherent prior to stopping or changing therapy.

In the context of low BMD and/or increased fracture risk following SCI, considerable uncertainty remains regarding the duration of treatment for specific pharmaceutical agents, as well as the thresholds and circumstances for changing therapeutic interventions. Nevertheless, given their obvious importance, in the absence of evidence specific to low BMD and/or increased fracture risk following SCI, the current literature for the general population and consensus opinion serve as the foundation for very weak recommendations regarding treatment duration.^{110,519}

8.0 FRACTURE MANAGEMENT

Preamble

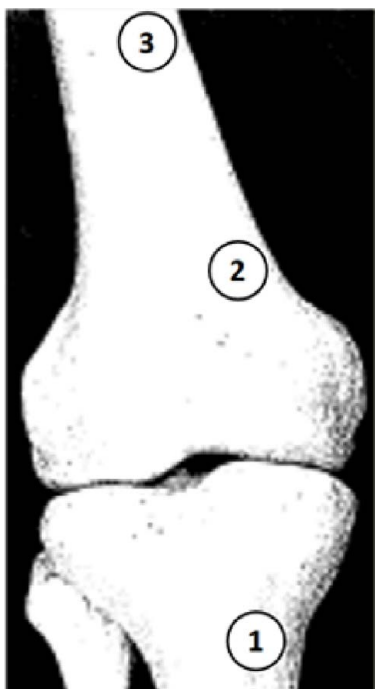
This section describes the special considerations for the management of individuals with lower extremity fracture among adults with spinal cord injury/disease (SCI/D). The importance of an initial orthopedic consultation to confirm the presence of a fracture is underscored. Specific medical and mobility considerations for rehabilitation teams to reduce fracture-related morbidity are discussed.

Context

Appropriate and timely post-fracture care strategies are needed to reduce fracture-related morbidity and mortality.^{259,520} Carbone²⁵⁸ has reported an increased risk for respiratory infection, pressure injuries, urinary tract infections, thromboembolic events, and delirium in the first month after fracture. The risk of mortality is greater in men over 50 years of age (hazard ratio [HR] 3.42, 95% confidence interval [CI] 2.75-4.25), in men with motor complete injury (HR 3.13, 95% CI 2.19-4.45), and in men with a high Charlson Comorbidity Index.²⁵⁷

Fragility fractures are defined in SCI as those that occur after a fall from standing or seated height or less, or in the absence of trauma such as during routine activities of daily living. The anatomical distribution of fragility fractures among individuals with SCI is summarized in Figure 8.1. In brief, lower extremity fractures of the proximal tibia, distal femur, and proximal femur are the most prevalent.^{36,258,520-523} Approximately 2%-5% of individuals with SCI experience a lower extremity fracture per year, with a lifetime incidence of 25%-50%.^{256,258,259,524} Fracture rates vary in the SCI population between 2.14 and 3.2 fractures per 100 patient-years.^{19,38,259,522,524} Women with SCI over age 50 are at higher risk of fracture than are younger women or men of any age (HR 1.56, 95% CI 1.18-2.06).¹⁶⁷ The total direct costs of lower extremity fracture after SCI are approximately \$6,070 USD (\$7,750 CAD).⁵²⁵ More than half of these fractures are related to low-impact injuries such as during transfers, particularly to and from a wheelchair,⁵²⁶ as well as other daily living skills such as dressing and bathing. For example, the combination of hip flexion/external rotation and concurrent knee flexion during dressing is a frequent torque that may lead to femur fractures. The key to optimal fracture management is early detection.

Figure 8.1. Anatomical distribution of fragility fractures among individuals with spinal cord injury, depicting (1) proximal tibia, (2) distal femur, and (3) femoral shaft anatomical sites.



Fracture Detection

Individuals with SCI and a lower extremity fragility fracture often present with mild regional lower limb swelling. The differential diagnosis for individuals with SCI/D who present with a swollen lower extremity includes fragility fracture, heterotopic ossification, venous thromboembolism (VTE), cellulitis, or deep tissue injury, alone or in combination. The wide differential diagnosis can contribute to delayed diagnosis of a fragility fracture.

X-rays are typically used to diagnose fracture or to demonstrate proper alignment and stabilization following fracture treatment. Clinicians with a high index of suspicion for fracture and negative X-ray results should further evaluate for fracture with computed tomography. In the event that it is not available, point-of-care ultrasound,⁵²⁷ repeat X-ray, triple-phase technetium-99M bone scan (scintigraphy), or magnetic resonance imaging may be used to detect a fracture.⁵²⁸ The choice of diagnostic imaging to confirm the fracture is in part determined by the anatomical location of the suspected fracture. Additional testing is particularly useful for detection of some hip, wrist, and distal lower extremity stress fractures. A venous Doppler ultrasound may be necessary to rule out VTE. Skin inspection, assessment of skin temperature, and a complete blood count may assist in identifying cellulitis. After a fracture is identified, an orthopedic consultation and consideration for implementation of thromboprophylaxis are needed.⁵²⁹

Lower Extremity Fracture

Recommendations

- 8.1 We recommend individuals with SCI and lower extremity long bone fragility or traumatic fracture undergo an orthopedic consultation.
1D
- 8.2 We recommend that clinicians actively identify individuals with SCI and a lower extremity fracture as having a diagnosis of osteoporosis, and be treated as having a moderate-to-high fragility fracture risk.
1B

- 8.3 One may use shared decision making to weigh the risks and benefits of surgical or conservative fracture management that accounts for the patients' values, preferences, health status, medical comorbidities, and available post-fracture attendant care resources.

2D

Clinical Consideration

8.3

Where feasible, discussion of the fracture management with the treating orthopedic surgeon, the patient, and the patient's care team (i.e., physiatrist, community care coordinator, occupational or physical therapist) is recommended to understand the postoperative care considerations.

- 8.4 We recommend when conservative fracture management is selected, clinicians prescribe soft, custom-molded, immobilization devices; bivalve the device; and provide heel and malleolar windows to prevent regional skin breakdown.

1D

- 8.5 We recommend that clinicians proactively assess the presence of leg edema and risk of skin injury and use multilayered compression wraps to help mitigate edema in individuals at risk.

1D

Rationale

Fracture care after SCI is optimally managed by an interprofessional team that includes an orthopedic surgeon, physiatrist, physical therapist, occupational therapist, and orthotist/orthopedic technician. There is agreement in the literature that lower extremity fragility fractures above the knee region should be managed operatively and that, below the knee region, the surgeon may consider operative intervention or fracture immobilization. The reader seeking advice regarding definitive fracture management

is directed to the Orthopaedic Trauma Association (OTA), "Treatment of Lower Extremity Fractures in Chronic Spinal Cord Injury: 2020 Delphi Consensus Recommendations."²⁷ Recently, the OTA convened a panel of experts to review the available evidence and recommend definitive fracture management (operative or conservative) on the basis of fracture anatomical location, fracture characteristics, and goals of maintaining function and minimizing the potential harms associated with delayed union, non-union, or fracture-related complications. Decisions regarding surgical vs. nonoperative management should consider the burden of implementation from the perspective of the individual with SCI and their medical comorbidities. In situations where fracture immobilization is required, precautions should be taken to ensure skin integrity and allow for regular visual inspection. This may include the use of soft, custom-molded, and bi-valved immobilizers (see Figure 8.2) or the incorporation of built-in reliefs or windows into casts over bony prominences such as the heel or malleoli.

Figure 8.2. Example of a custom-molded immobilization device used in conservative fracture management (soft lining is not visible in photo).⁵³⁰



This review and the associated recommendations pertain to the rehabilitation and primary care of individuals with SCI following definitive fracture diagnosis and management by an orthopedic surgeon.

Few studies to date have investigated the impact of fracture management on functional outcomes and patient-reported quality of life during the healing process. Instead, the literature describes high rates of medical complications and discusses strategies to mitigate adverse events following fracture. Following operative and conservative fracture management, complications may include the following: autonomic dysreflexia,^{520,531} infection,^{522,532,533} pressure injuries,⁵³⁴ compartment syndrome,⁵³⁴ amputation, spasticity,^{520,535} swelling,⁵³⁵ shoulder pain,⁵³⁶ depression,⁵³⁷ deconditioning,⁵³⁸ and pseudoarthrosis.^{520,533,534}

The risk of pseudoarthrosis is higher among individuals with SCI who sustain a fracture of the proximal femur compared with those whose fracture is located at the tibia (odds ratio [OR]=64.87, $p<0.00006$).⁵³⁴ The odds of developing pseudoarthrosis are highest in those with a class B fracture according to the AO/OTA classification system⁵³⁹ (OR=5.23, $p<0.028$)⁵³⁴ and in those undergoing conservative fracture management (OR=5.68, $p<0.036$).⁵³⁴ Although successful healing occurs with most fractures, malalignment and segmental shortening are common with pseudoarthrosis or failure of fusion.⁵⁴⁰ Pin site infections have been reported among individuals who require external immobilizers for fracture fixation.⁵⁴¹ Shoulder ailments may result from immobility and provision of leg orthoses/immobilization devices that inhibit transfers and bed mobility. Further, short-term increases in the need for attendant care during fracture healing are common.

There is a paucity of information regarding the management of delayed union or non-union lower extremity fragility fractures among individuals with SCI in general, as well as the role of the commercially available Smith & Nephew Exogen 4000+542 low-intensity pulsed ultrasound device, specifically for facilitating fracture healing.

Changes in Mobility

Recommendations

- 8.6 We recommend that clinicians prescribing immobilization devices to wheelchair users with SCI/D and lower extremity fracture consider prescribing an elevating leg rest and/or additional attendant care supports.

1D

Clinical Consideration

8.6

Clinicians should consider an assessment of all therapeutic support surfaces (i.e., cushion, wheelchair, therapeutic mattress) used in supporting the immobilized leg.

Clinicians should conduct a thorough evaluation of transfers, bed mobility, and activities of daily living, as alternate transfer techniques or equipment may be required (i.e., Hoyer lift). Rental of a wheelchair that allows for seat-to-back angle adjustments may be necessary for those with hip fracture, who are unable to sit at 90 degrees.

Occupational therapists should assess dressing technique, retrain patients as needed, and consider provision of additional assistive devices during the time of fracture healing in order to reduce bone torque/resistance during performance of dressing/bathing and bowel/bladder management routines.

Rationale

Individuals with SCI who require lower extremity immobilization devices/casts may require additional attendant care supports to assist with level transfers, dressing, bathing, toileting and bowel/bladder programs, and skin care during the period of fracture immobilization. In some cases, assistance with grocery shopping, meal preparation, laundry, and housekeeping may also be appropriate. Involvement of a social worker and/or occupational therapist to assist with a needs assessment is indicated. The need for new or modified assistive devices or equipment should be anticipated following lower extremity fracture.⁵²⁶ Provision of an elevating leg rest to reduce edema and a lower extremity cast/immobilization device to stabilize a fracture will shift the individual's center of gravity forward and increase their risk of falling forward. Individuals with high paraplegia/tetraplegia often require a chest strap and assistance with transfers during this time to avoid falls and further injury. Alterations in mobility after fracture can result in an increased risk of VTE and/or overuse injuries of the shoulders, which may lead to joint pain or other new upper extremity ailments. This review and the recommendations herein pertain to VTE prophylaxis in the setting of lower extremity fracture following chronic SCI.

Medical Care Beyond Fracture Management

Venous Thromboembolism Prophylaxis

Recommendations

- 8.7 We recommend, for individuals with chronic SCI who develop a new hip, femur, or tibia fracture, that clinicians routinely assess their risk of venous thromboembolism.
1C

Clinical Consideration

8.7

We consider patients with chronic SCI who develop a major lower extremity fracture to be at increased risk for VTE. As a key component in a comprehensive fracture management program, we believe that anticoagulant thromboprophylaxis should be provided routinely, at least during readmission and rehabilitation care, with consideration given to post-discharge thromboprophylaxis. We believe that a similar consideration should be given to patients who are not admitted. The options include subcutaneous low molecular weight heparin (LMWH), including enoxaparin, dalteparin, or tinzaparin, or a direct oral anticoagulant (DOAC), including rivaroxaban, apixaban, edoxaban, or dabigatran.

Contraindications for the use of anticoagulant-based thromboprophylaxis include high risk for bleeding or platelet count less than 30 109/L. Patients who have had heparin-induced thrombocytopenia in the past should not receive LMWH unless this has specifically been supported by a hematologist or thrombosis specialist.

Although we recommend LMWH or a DOAC as the preferred thromboprophylaxis options, there may be situations in which warfarin or aspirin are acceptable options.

- 8.8 We recommend, for individuals with chronic SCI who develop a new hip, femur, or tibia fracture, that clinicians routinely provide anticoagulant

thromboprophylaxis with low molecular weight heparin (LMWH) or a direct oral anticoagulant (DOAC) if there are no contraindications
1C

or

Obtain the advice of a health professional with expertise in the area of thromboprophylaxis, such as a SCI rehabilitation physician, hematologist, thrombosis specialist, or internist.
1D

- 8.9 We recommend, for individuals with chronic SCI who develop a new hip, femur, or tibia fracture, that thromboprophylaxis start as soon after the fracture as is feasible.
1C

- 8.10 One may consider, for individuals with chronic SCI who develop a new hip, femur, or tibia fracture who are admitted to hospital, that thromboprophylaxis continue at least until discharge from acute care and rehabilitation with consideration of at least 2-4 weeks.
2D

- 8.11 One may consider, for individuals with chronic SCI who develop a new hip, femur, or tibia fracture who are not admitted to hospital, that thromboprophylaxis continue for at least 2-4 weeks.
2D

Rationale

It is well established that patients with acute SCI have the highest risk of VTE among hospitalized patients and that they warrant routine “aggressive” thromboprophylaxis.⁵⁴³⁻⁵⁴⁶ The risk of VTE declines after the acute and rehabilitation phases of SCI, although the risk remains greater than for age-matched controls without SCI indefinitely.⁵⁴⁷⁻⁵⁵² Among a cohort of 94 individuals with SCI, the incidence of VTE in the first 3 months was 34 per 100 patient-years and 0.3 per 100 patient-years thereafter.⁵⁵³ The rates of VTE in 12,584 SCI patients at 3 months, 6 months, and 12 months after injury were reported to be 34%, 1.1%, and 0.4%, respectively.⁵⁵¹

The reasons for persistent thrombosis risk in SCI patients include the following:

- Venous stasis related to chronic immobilization
- Reduced venous outflow secondary to compression of the common femoral veins associated with prolonged sitting in a wheelchair
- Decreased endogenous tissue plasminogen activator release from the venous endothelium
- Leg injuries that are not appreciated by patients who have sensory deficits
- Increased inflammatory stress prior to fracture onset⁵⁵⁴⁻⁵⁵⁸
- Hematologic risk factor related to a novel circulating antibody that specifically blocks the high-affinity prostacyclin platelet receptors⁵⁵⁹
- Elevated thrombin generation and platelet-derived growth factor release from platelets⁵⁶⁰
- Markedly impaired insulin-induced nitric oxide production by platelets⁵⁶¹
- Patients with fractures of the lower extremity have repeatedly been shown to have increased risk of VTE.⁵⁶² In a systematic review of patients with acute leg immobilization, deep vein thrombosis was found in 21% of the 416 patients with fractures, in 15% of the 429 patients with plaster casts, and in 26% of the 350 patients who had surgical repair.⁵⁶² In the same review, LMWH was shown to reduce proximal deep vein thrombosis by 61% and symptomatic VTE by 91% compared with no prophylaxis. A randomized controlled trial that compared enoxaparin with rivaroxaban as thromboprophylaxis in 3,604 patients following non-major lower extremity orthopedic surgery showed a 75% reduction in the risk of symptomatic VTE with rivaroxaban vs. enoxaparin and no difference in bleeding.⁵⁶³ In patients with major pelvic trauma, femoral fractures, or who are hospitalized with other leg fractures, anticoagulant thromboprophylaxis is usually given while in hospital (including rehabilitation). Although post-discharge prophylaxis is commonly used for 10-28 days in patients with hip fracture, thromboprophylaxis after hospital care for patients with isolated lower extremity fractures is controversial.^{564,565}

VTE in Patients with Chronic SCI who Develop Leg Fracture

Few studies have reported VTE risks in patients with chronic SCI who develop a leg fracture, although SCI is a risk factor for VTE in such patients.⁵⁶⁴ Among 1,027 men enrolled in the Veterans Affairs Spinal Cord Dysfunction Registry who developed lower extremity fractures at least 2 years after the SCI, the risk of thromboembolic events was increased compared with that in a propensity-matched SCI group without fractures.²⁵⁸ The excessive VTE risk decreased over time from the fracture: HR 2.6 (95% CI 1.1-6.3) at 1 month, 1.2 (95% CI 0.5-2.7) at 6 months, and 1.1 (95% CI 0.4-3.0) at 1 year.

Prevention of VTE in Patients with Chronic SCI Who Develop Leg Fracture

We are not aware of any clinical trials or practice guidelines that specifically address thromboprophylaxis in patients with chronic SCI who develop acute lower extremity fracture. However, these patients likely have a higher risk of VTE than do patients without SCI who have similar injuries. The 2016 Consortium for Spinal Cord Medicine guidelines recommend that individuals with chronic SCI who are hospitalized for medical illnesses or surgical procedures receive thromboprophylaxis during the period of increased risk.⁵⁴³ We recommend that routine anticoagulant thromboprophylaxis be used in these patients. The options, based on a large volume of evidence in other high-risk patients, are LMWH or a DOAC. LMWH has been well studied in numerous patient groups, including those having major orthopedic surgery, who are recovering from major trauma, or who have an acute medical illness.^{566,567} DOACs have also been well studied in orthopedic surgery and as post-discharge prophylaxis in medical patients.⁵⁶⁸⁻⁵⁷¹ The advantages of DOACs compared with LMWH are their greater efficacy in clinical trials and in clinical practice, their oral route, and their reduced cost.^{563,572,573}

There is major uncertainty about the optimal duration of thromboprophylaxis in individuals with SCI who have leg fractures. From studies in patients who have undergone hip or knee replacement or hip fracture repair, we suggest that thromboprophylaxis continue for at least 2-4 weeks after fracture. Other criteria that may be used to determine duration of thromboprophylaxis include the resumption of preinjury mobility or evidence of fracture healing.

Autonomic Dysreflexia

Recommendations

- 8.12 We recommend that clinicians monitor individuals with a neurological level of T6 or above and a recent lower extremity fracture for symptoms of autonomic dysreflexia (AD).
1D

Clinical Consideration

8.12

AD symptoms may include a ≥ 20 mmHg rise in systolic blood pressure (above the individual's baseline) alone or in combination with sweating, blurry vision, nasal congestion, piloerection, anxiety, headache, and/or chest pain.

- 8.13 We recommend that in individuals with persisting AD symptoms and elevated blood pressure at or above 150 mmHg systolic prior to catheterization, clinicians consider rapid-onset and short-duration pharmacological management to reduce the systolic blood pressure without causing hypotension.¹
1D
- 8.14 We recommend that individuals with persisting AD symptoms who are not responding to removal of an identified noxious stimulus be transferred to a monitored setting where oral, topical, or intravenous medications (nitroglycerin, hydralazine, or nifedipine) can be administered to acutely lower their systolic blood pressure.
1D
- 8.15 We recommend, for those at risk for AD, that clinicians provide analgesia for nociceptive pain to prevent AD in the first 3-5 days after fracture and implementation of definitive fracture management.
1D

Rationale

Non-SCI clinicians should be aware that individuals with SCI and a neurological level at or above T6 have low baseline systolic blood pressures of approximately 100 mmHg and are at risk for a rare

and life-threatening condition called autonomic dysreflexia (AD). Common causes of mild-to-severe AD after a fracture include a cast or fixation device that is too tight, causing tissue injury; untreated regional nociceptive pain; undetected cellulitis or a VTE; and/or bladder or bowel distension. AD has been reported in individuals with fracture below the level of injury, with motion at the fracture site being reported as a possible noxious stimulus.⁵³⁸ Many individuals with SCI have impairments in cutaneous sensation; however, they may have variable preservation of the autonomic nervous system that regulates the heart muscle, smooth muscles, intestines, and glands, and they may have intact visceral sensation, creating multiple plausible mechanisms for new nociceptive pain or neuropathic pain exacerbation.

The affected individual may initially present with sweating above the level of injury or restlessness. He/she may then experience ≥ 20 mmHg elevation in systolic blood pressure above the patient's baseline, and a decrement in the heart rate. The initial treatment for AD is to identify the source of the noxious stimulus and remove it. For treatment of mild AD, sit the patient up or raise the head of their bed; loosen any tight clothing, braces, socks, stockings, or bandages; and check the skin for redness, pressure injury, or ingrown toenails. If symptoms persist, drain the patient's bladder with an intermittent or Foley catheter. Specific noxious stimuli that cause AD after a fracture may require the removal of a cast or treatment of underlying cellulitis. If the elevations in systolic blood pressure persist and are associated with a headache or chest pain, this becomes a medical emergency that requires transfer to a monitored setting and urgent administration of drug therapy to reduce the systolic blood pressure. Medications with rapid onset and short duration of action, including nitroglycerin spray, paste, or patches; nifedipine; or hydralazine are most commonly recommended to reduce blood pressure if systolic blood pressure exceeds 150 mmHg for more than 20-30 minutes while working to remove the noxious stimuli and monitoring for hypotension.¹ The occurrence of AD symptoms after fracture should necessitate serial monitoring, and, in cases in which AD progresses and persists, immediate medical treatment is required to prevent heart attack or stroke due to the sustained dramatic elevations in systolic blood pressure.¹

Timing of Osteoporosis Therapy

Recommendations

- 8.16 One may consider initiation of osteoporosis treatment soon after fragility fracture (see Sections 5.0, 6.0, and 7.0).

2D

Clinical Consideration

8.16

An adequate intake of calcium and vitamin D through dietary intervention or routine supplement ingestion are part of a holistic fracture management plan. See Section 5.0 for specific recommendations on dietary intake of calcium and vitamin D.

There is little evidence to guide decisions regarding initiation of osteoporosis therapy after a fragility fracture in the SCI population. Initiation of antiresorptive therapy with medication need not be postponed during fracture healing. Early administration of BPs after surgery does not delay fracture healing in the general non-SCI population.⁵⁷⁴

Rationale

Many patients who present for hospital admission with a lower fragility fracture are not recognized as having osteoporosis and a high fracture risk that requires therapy. After a patient is medically stable, bone mineral density testing and consideration of therapy to reduce future risk of fracture are recommended (see Sections 5.0, 6.0, and 7.0).

Rehabilitation Care Beyond Definitive Fracture Management

Pressure mapping readings across the buttocks will show increases in peak pressures over ischia when a leg is positioned in an elevated position either by an elevated leg rest or subsequent limb elevated by a leg stabilizer device.

Following an injurious fall, it is important that an individual fall risk assessment take place and education programs be implemented to increase an individual's confidence and ability to engage in community mobility. See Section 1.0 for specific fall risk assessments and recommendations regarding how to mitigate fear and increase balance confidence.

Recommendations

- 8.17 We recommend that following fracture healing, clinicians refer individuals with SCI for a comprehensive mobility assessment that includes transfer training, wheelchair skills upgrading and reconditioning, and bracing/orthotic assessment, as appropriate (see Section 1.0).

1D

- 8.18 We recommend that clinicians aim to return individuals with SCI to their premorbid hip, knee, and ankle range of motion after fracture healing.

1D

Clinical Consideration

8.18

Botox, serial casting, or passive standing may be required to achieve the goal of restoring lower extremity range of motion.

- 8.19 One may consider that decisions to progress to weight bearing and loading be jointly planned between the treating health care professionals (e.g., orthopedic surgeon, physiatrist, physical therapist) and the individuals with SCI who have a recent fracture in order to reduce the risk of further injury proximal or distal to the fracture site.

2D

Clinical Consideration

8.19

Physical therapists should introduce weight bearing followed by strength training after achieving restoration of lower extremity passive range of motion where feasible.

- 8.20 We recommend that clinicians refer individuals with SCI who are wheelchair users with changes in pelvic or lower extremity alignment, residual deformity, limb length discrepancy, or seating posture after a fracture for a seating reassessment.

1D

Clinical Consideration

8.20

Increase in frequency of skin inspection of the buttocks, increase in weight shifting, or reduction of sitting time should be considered to avoid development of a pressure injury.

- 8.21 One may consider referring individuals with SCI who are ambulatory with changes in pelvic or lower extremity alignment, residual deformity, or limb length after fracture for a bracing/orthotic assessment.

2D

Clinical Consideration

8.21

Careful attention to the patient's positioning is needed to reduce risk of pressure injury when seated or lying with a brace or orthosis.

Twice daily skin inspection is recommended prior to donning or doffing an orthotic or brace each day to limit the risk of pressure injury.

Rationale:

There is a dearth of evidence regarding optimal post fracture rehabilitation care among individuals with SCI/D. Among ambulators and wheelchair users alike, monitoring of skin integrity within the fixation device to detect pressure injury or cellulitis during fracture healing and careful attention to positioning when seated, and in bed, are needed to prevent tissue injury of the affected and unaffected proximal limbs. The mobility needs of wheelchair users and ambulators are distinct during the fracture healing process; however, following fracture healing both require monitoring for deconditioning, tissue injury, alterations in joint ROM, transfer technique, and their mobility. Among wheelchair users, pressure map readings across the buttocks will show increases in peak pressures over the ischia when a leg is positioned in an elevated position by an elevated leg rest, cast or orthosis. A seating assessment, with pressure mapping, will readily identify individuals at risk for developing an ischial region or a posterior pelvic pressure injury.

Early after definitive fracture treatment, there is an increased risk of fracture above or below the fixation device or hardware. Thus, decisions regarding return to weight bearing and loading progressions need to be made jointly between the orthopedic surgeon and members of the care team with knowledge of joint ROM to avoid further injury, prevent secondary health conditions and promote functional restoration as soon as feasible.

Many individuals with SCI/D develop fractures, which result in mal-union, or delayed union and when managed conservatively require many months to heal. Following fracture healing, members of an interprofessional team (for example a physical therapist, occupational therapist, nurse and physiatrist) should assess the individual with SCI/D for new impairments or impediments to their mobility with potential adversely impact their long term health or mobility. Common impairments include global deconditioning, limb shortening, contracture, concurrent infection, reduced ROM in the joint above and below the fracture site, altered transfer technique, mood disorders and fear of falling. After an injurious fall, it is vital than an individual fall risk assessment take place. Following these assessments, members of the interprofessional rehabilitation team should co-develop a care plan which includes educational interventions to increase the individual's mobility confidence, alter or replace mobility devices and orthoses, adjust wheelchair seating and provide therapy intended to return the individual to their premorbid level of function or as close to it as feasible in a timely manner. Readers may find additional information within the Delphi Consensus manuscripts from the Orthopedic Trauma Association on Fracture Management after SCI.⁵⁷⁵

Direction for Future Research

Preamble

This section provides a high-level overview of key research dilemmas and opportunities to enhance care through the conduct of methodologically rigorous studies that address specific gaps in knowledge and clinical implementation pertaining to bone health and osteoporosis management among individuals living with spinal cord injury/disease (SCI/D). The initial section addresses gaps that span a number of key concepts and are broadly applicable, followed by specific recommendations pertinent to each of the sections of the guideline (as appropriate). Finally, specific recommendations are provided related to increasing knowledge and expanding implementation of bone health measures for the SCI/D population.

Key Concepts for the Research Community

Future research regarding bone health and osteoporosis management among individuals living with SCI/D necessitates the use of low risk of bias randomized control trials (RCTs), prospective multicenter pragmatic studies, and other high-quality research methods. Clinical research in the field of SCI in general, and osteoporosis specifically, has suffered from a number of design and methodological limitations largely due to the relatively small population of persons with SCI/D available for enrollment in research studies and clinical trials, specifically in single-site studies. Despite this limitation, researchers should strive to use the strongest designs and methods possible to improve the validity and generalizability of findings. Given the sample size issues evident throughout this guideline, multisite studies with an adequate sample size are warranted. In addition, studies should ensure an appropriate duration of assessment to determine the effects of the intervention, and assessors should be blinded to treatment allocation. All health care professionals who engage in research should receive training on routine reporting of safety and adverse events, specifically fracture. Finally, granting agencies and journal editors should be discerning in considering the design, methodological details, and quality of applications or articles related to SCI/D.

Studies specific to bone health should address the following design, equity, and outcome considerations:

- Design studies that include racially diverse populations with sufficient sample size to identify factors that may differ by race.
- Include men and women with SCI/D in order to identify and evaluate factors that may differ by sex.
- Conduct studies of sufficient sample size to allow stratification by sex in order to address gender-specific risk factors for bone loss in women with SCI and include premenopausal and postmenopausal women to better understand and address these risks.
- For studies that address fracture risk reduction, select anatomical regions for measurement that are the most susceptible to fracture (i.e., total hip, femoral neck, distal femur, and proximal tibia).
- Study outcomes, specifically those using dual-energy X-ray absorptiometry (DXA), should include absolute values and percentage change.
- Evaluate fracture risk reduction instead of or in addition to regional maintenance or change in absolute bone mineral density (BMD, g/cm²), the typical surrogate outcome.
- Standardize concurrent administration of calcium and vitamin D supplements when evaluating the efficacy of interventions.
- Follow up with study participants to document short- and long-term outcomes in clinical trials of sufficient sample size and study duration of at least 12 months if BMD by DXA is the primary outcome measure.
- Use advanced imaging techniques in interventional RCTs, including quantitative computed tomography (QCT) and peripheral quantitative computed tomography (pQCT) to describe the changes in trabecular and cortical volumetric BMD and bone architecture and geometry.

Laboratory Screening

Researchers should determine the availability of standardized biomarkers of bone turnover, using comparative laboratory techniques that include normative reference values, to advance our understanding of the underlying systemic changes that accompany changes in bone imaging metrics at specific time points.

Specific research questions include the following:

- Determine whether laboratory measurement of bone biomarkers (serum, urine, sputum, etc.) identifies the effectiveness of treatment for increasing BMD and lowering fracture rates and incident fractures.
- Determine whether secondary causes of osteoporosis identified by laboratory screening are associated with low or declining BMD and incident fractures.
- Determine the optimal serum levels of 25-hydroxyvitamin D (25-(OH)D), intact parathyroid hormone (PTH) and bioavailable testosterone for skeletal health among males and females with SCI/D and identify effective treatment regimens to maintain BMD and reduce risk of fracture.

Measurement of Bone Density

- Quantify risk of incident fracture based on DXA-derived bone density assessments at both traditional (femoral neck, total hip) and SCI-specific skeletal sites (distal femur, proximal tibia) and the contributions of demographic, lifestyle, and SCI-related characteristics.
- Establish a large healthy reference database at SCI-specific DXA sites (distal femur and proximal tibia) and standardize acquisition and analysis protocols; DXA manufacturer engagement is recommended. Studies should characterize reliability and least significant change for assessment sites.
- Define clinically important changes in QCT and pQCT variables and establish QCT- and pQCT-based diagnostic criteria related to fracture risk; a large healthy reference database at pQCT sites is needed.
- Determine the degree to which differences in cortical vs. trabecular compartments measured with pQCT reflect location-specific or compartment-specific differences in bone metabolism.
- Investigate the clinical importance of emerging measurements to standardize and define additional outcome metrics and to better link pQCT and QCT metrics to fracture risk.

Nutrition

- Determine the efficacy and toxicity of the proposed vitamin D repletion algorithm.
- Explore the relationship of impaired glucose tolerance and diabetes to BMD and fracture risk.
- Consider racial differences in vitamin D and calcium requirements and their relation to BMD and fracture risk.
- Examine whether optimal levels of serum 25-(OH)D and intact PTH for skeletal health differ by race.

Rehabilitation Therapy

For biomechanical loading therapies, including electrical stimulation and weight-bearing, determine the degree to which training volume is related to changes in BMD and whether there is an upper limit to training volume or duration, as well as the differential effects on different anatomical bone compartments and for different bone regions. Studies of loading interventions should identify the following:

- Effective training strategies by conducting routine reporting of load during interventions
- Effective electrical stimulation parameters (i.e., frequency, duration, and amplitude) for muscle activation that generate sufficient load while reducing time to fatigue
- Effective relative contributions of training volume (frequency and duration), load, and optimal stimulation parameters that reduce muscle fatigue and safely optimize bone loading
- Minimum load threshold that is sufficient for preserving or augmenting BMD or bone quality
- Progression of training load and stimulation parameters, which should be reported for specific participants in addition to ranges or averages per group

Research is needed in these areas:

- Investigation of the effect on bone density and fracture risk of treatments that combine loading with pharmacological and/or nutritional interventions
- Evaluation of safety of electrical stimulation protocols as related to aging and age-related bone loss

- Evaluation of the potential benefits of overground walking, including weight-supported and treadmill training, with sufficient frequency and duration of loading

Pharmacological Therapy

- Establish the efficacy of pharmacological prophylaxis for secondary bone mineral density loss following acute SCI, stratified by demographic variables such as age, gender, race, and level of neurological impairment.
- Explore the risks and benefits of continuing pharmacological therapies that prevent/decrease bone loss in acute SCI beyond the acute phase (i.e., beyond 18 months post-injury).
- Establish the efficacy of pharmacological treatment of reduced BMD and osteoporosis in chronic SCI. Specifically, studies should determine the effect of promising pharmacological interventions to prevent further bone loss, increase bone density, or prevent fragility fractures of the hip, distal femur, or proximal tibia.
- Conduct clinical trials on the efficacy of antiresorptives, anabolic agents that promote osteoblast activity, and interventions that combine antiresorptives, anabolic agents, and mechanical interventions.

Fracture Management

- Evaluate the efficacy of surgical and medical management strategies for reducing and preventing fracture-related morbidity.
- Determine whether low levels of electrical stimulation of muscle can improve fracture healing, especially for a non-healing lower extremity fracture.
- Explore the patient experience in terms of the effects of having and healing from a lower extremity fracture. Investigate whether quality of life differs by how the fracture is managed (surgical vs. medical management).

Education and Training

Further education and training, for both health care professionals and individuals living with SCI, is recommended to address potential gaps in

knowledge and practice in the field of bone health and osteoporosis management after SCI.

Education on the identification of medical conditions associated with secondary causes of osteoporosis by laboratory screening studies should be done as part of training programs, including continuing medical education programs, for physiatrists, with additional postgraduate training and clinicians caring for individuals with SCI.

Physicians need to familiarize themselves with best practices for assessing bone mineral density, including DXA, pQCT, and/or QCT; to understand the options and limitations for selecting measurement sites; and to have the ability to interpret the bone quality outcomes and to regularly monitor an individual's bone health.

Physiatry training programs should include education regarding the adequacy of calcium and vitamin D intake and the use of validated 25(OH)D assays.

Health care providers and individuals with SCI should discuss the anticipated declines in BMD in the lower extremities and how this increases the risk for future fragility fractures, as well as the importance of periodic DXA scanning of the total hip, distal femur, and proximal tibia to determine absolute fracture risk. Individuals with SCI should consult with an SCI-specific health care provider and receive appropriate education and resources before engaging in electrical stimulation therapy or other interventions to maintain or improve bone health after SCI.

Prior to the provision of rehabilitation therapy, education and training is needed for the safety of individuals with SCI. Training programs in rehabilitation science and physiatry need to include curriculum regarding the principles and practices of post-fracture care for individuals with SCI.

Implementation of Clinical Practice Guidelines

Clinical practice guidelines (CPGs) are intended to facilitate standardization of care delivery and provide the best available evidence regarding how to manage a specific health condition. Implementation of the enclosed bone health and osteoporosis management CPG requires not only the dissemination of the guidelines to relevant providers, but also the

identification of barriers and facilitators to applying the guideline recommendations in practice. Barriers may include lack of appropriate equipment or software (e.g., not having the software needed to assess bone mineral density at the distal femur and proximal femur) and/or policies that limit testing (e.g., testosterone) or medication doses (e.g., calcium). Leadership support, use of clinical champions, clinical decision support tools, and giving feedback to providers on how well they are doing in routinely applying the recommendations are some of the ways that the health care systems can facilitate the integration of guidelines into ongoing practice. We trust that this CPG will stimulate implementation champions at your center to take up the banner and help facilitate a meaningful reduction in lower extremity fractures and fracture-related morbidity and mortality.

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Appendices

Appendix A: Panel Conflict of Interest Statement

CONSORTIUM FOR SPINAL CORD MEDICINE

Steering Committee Member and Guideline Development Panel Member please read the following policies on Conflicts of Interest and Confidentiality and sign below to indicate acceptance.

POLICY ON CONFLICTS OF INTEREST

The Consortium for Spinal Cord Medicine (hereafter referred to as “the Consortium”) is a collaboration of professional and consumer organizations funded and administered through Paralyzed Veterans of America (hereafter referred to as “PVA”). PVA wants to ensure that regular business of the Consortium’s Steering Committee and the guideline development process are free from conflicts of interest. PVA recognizes that those on the Steering Committee and Guidelines Development Panels are involved in a variety of organizations and projects, and may hold financial investments which might create actual or potential conflicts of interest or the appearance of a conflict (each a “conflict” or “conflict of interest”).

To achieve that result, the following policy is adopted:

1. **Applicability.** This Policy applies to the Consortium’s Steering Committee Members, including the Chair and Vice-Chair, in addition to those members on the Guideline Development Panels (collectively, “Covered Persons”).
2. **Term.** This agreement is effective for the term the Covered Person is a member of the Steering Committee and/or a Guideline Development Panel, notwithstanding how active or passive a role he or she may play as a member of the Steering Committee or a Guideline Development Panel.
3. **Determining the Existence of a Conflict.** The guidelines set forth below shall be used to determine the existence of a conflict. The guidelines are meant to be illustrative and not

exclusive; a conflict may exist even though the situation in question is not included below. Each Covered Person bears the personal responsibility for initially determining if a conflict of interest exists with respect to such Covered Person. If a Covered Person has any questions regarding the existence of a conflict, such Covered Person should promptly contact the Steering Committee Chair.

4. Guidelines for Determining Existence of Conflict.

A conflict may exist if the Covered Person is unduly influenced by others (i.e. his/her spouse, parent, child, or other individual with whom such Covered Person has a close personal, business or professional relationship (including persons with whom such Covered Person is a partner, shareholder in a closely held corporation, coauthor or other close professional coworker or colleague) to the detriment of and against the mission of the Consortium, the Steering Committee, the Guideline Development Panels, and PVA.

5. **Disclosure of Conflict: Recusal.** If a Covered Person determines that a conflict exists, then he or she shall notify immediately the Steering Committee Chair or the Director of PVA’s Research and Education Department. The Chair, with input from the Director of Research and Education, shall determine whether a conflict exists (except that in cases of conflicts involving the Chair, the Vice Chair shall decide). The decision on conflicts and the basis of that decision shall be reported to the Steering Committee and recorded in the minutes. Unless otherwise determined by the Chair (or, as appropriate, the Vice Chair) in individual cases, if a conflict is found to exist, the affected person shall recuse himself/herself from all discussions, determinations and votes with respect to the matter with which the conflict exists, and shall excuse him/herself from all meetings at which any discussions regarding the matter take place. Following the termination of such determinations and discussions involving the conflict, such Covered Person may rejoin the meeting.

POLICY ON CONFIDENTIALITY

In the course of conducting regular business for the Consortium and/or Guideline Development Panel(s), Steering Committee Members and Panel Members may receive and be given access to confidential information concerning PVA or another entity working with the Consortium. To ensure that the confidentiality of the information will be maintained, the following Policy on Confidentiality is adopted.

1. **Applicability.** This Policy applies to the Consortium's Steering Committee Members, including the Chair and Vice-Chair, in addition to those members on the Guideline Development Panels (collectively, "Covered Persons").
2. **Term.** This agreement is effective for the term the Covered Person is a member of the Steering Committee and/or a Guideline Development Panel, notwithstanding how active or passive a role they may play as a member of the Steering Committee or a Guideline Development Panel.
3. **Definition of Confidential Information.** "Confidential Information" means (i) all written business, financial, technical and scientific information relating to the Consortium and which PVA has marked conspicuously "CONFIDENTIAL," "PROPRIETARY," or similar marking; or (ii) oral information which is specified as confidential by the Steering Committee and/or PVA. All documents derived during the guideline development process are confidential, and they remain so until 1) the document has been approved for publication by a vote of the Steering Committee and 2) the document is released by PVA as a printed document.

"Confidential Information" shall exclude information which (a) is in the public domain at the time of disclosure; (b) is in the possession of the Consortium (including any Covered Person) free of any obligation of confidence prior to the time of disclosure; (c) though originally within the definition of "Confidential Information", subsequently becomes part of the public knowledge through no fault of the Consortium (including any Covered Person), as of the date of its becoming

part of the public knowledge; (d) though originally within the definition of "Confidential Information", subsequently is received by the Consortium (including any Covered Person) without any obligation of confidentiality from a third party who is free to disclose the information, as of the date of such third-party disclosure; or (e) is independently developed by the Consortium without the use of any Confidential Information.

4. **Nondisclosure of Confidential Information.** Each Covered Person agrees not to disclose to any person outside the Consortium or its affiliates (including for these purposes Chapters and International Affiliates) any Confidential Information, except as provided below. Each Covered Person agrees that he/she will use the Confidential Information only for the purpose of Consortium business. Notwithstanding the foregoing, a Covered Person may disclose the Confidential Information (i) to employees, professional advisors, volunteer scientists and other Covered Persons asked to participate in Consortium business, consultants and agents of the Consortium who have a need to know and who have been informed of this Policy on Confidentiality; or (ii) to the extent required by a court order or by law. Each Covered Person shall use the same degree of care, but not less than a reasonable degree of care, that he/she uses to protect the Consortium's own most highly confidential information to prevent any unauthorized or inadvertent disclosure of Confidential Information.

Any individual having question(s) concerning this policy or its applicability in a given situation(s) should address those question(s) to the Director of Research and Education (PVA).

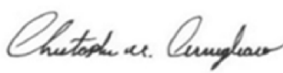
5. **Return of Confidential Information.** Each Covered Person agrees to return to the Chair of the Steering Committee or the Director of Research and Education, all tangible materials incorporating Confidential Information made available or supplied to such Covered Person and all copies and reproductions thereof upon request of the Chair of the Committee and/or the Director of Research and Education (PVA).

CERTIFICATION REGARDING CONFLICTS OF INTEREST and CONFIDENTIALITY OF INFORMATION

Each Covered Person agrees to comply with the provisions of these Policies so long as he/she is a Covered Person. By signing, you are confirming that you have read and understand the above Policy on Conflicts of Interest and Confidentiality and agree to abide by same during all times that you are a Covered Person, as defined in the Policy.


Anthony Burns, MD, MSc


Laura D. Carbone, MD, MS

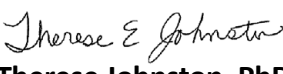

Christopher M. Cirnigliaro, PhD


B. Catherine Craven, MD, MSc


Kristine Cowley, PhD


Janice Eng, PhD, PT

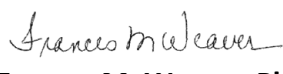

Gail Forest, PhD


Therese Johnston, PhD, PT


Sarah Morgan, MD, RD


Leslie Morse, DO


Karen L. Troy, PhD

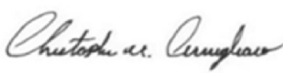

Frances M. Weaver, PhD

CERTIFICATION REGARDING CONSORTIUM POLICIES AND PROCEDURES

Each Covered Person agrees to comply with the provisions of the policies and procedures outlined in the Clinical Practice Guideline Orientation Manual so long as he/she is a Covered Person. By signing, you are confirming that you have read and understand the Clinical Practice Guidelines Orientation Manual Policies and Procedures and agree to abide by same during all times that you are a Covered Person.


Anthony Burns, MD, MSc


Laura D. Carbone, MD, MS

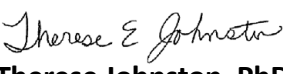

Christopher M. Cirnigliaro, PhD


B. Catherine Craven, MD, MSc


Kristine Cowley, PhD


Janice Eng, PhD, PT

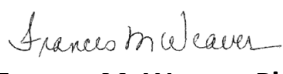

Gail Forest, PhD


Therese Johnston, PhD, PT


Sarah Morgan, MD, RD


Leslie Morse, DO


Karen L. Troy, PhD


Frances M. Weaver, PhD

Appendix B: Search Methodology and Terms Example

Key Question 2: Peripheral Quantitative Computed Tomography (pQCT) Validity

MEDLINE/EMBASE (Human and English Applied)

(computer tomography OR peripheral quantitative computed tomography OR quantitative computed tomography OR CT OR pQCT OR QCT) AND (bone mineral density OR volumetric bone mineral density OR bone mineral content OR BMD OR vBMD OR BMC) AND (spinal cord injur* OR tetrapleg* OR quadripleg* OR parapleg* OR spinal cord impaired OR spinal cord lesion)

CINAHL (Human and English Applied)

(peripheral quantitative computed tomography OR quantitative computed tomography OR pQCT OR QCT) AND (bone mineral density OR volumetric bone mineral density OR bone mineral content OR BMD OR vBMD OR BMC) AND (spinal cord injur* OR tetrapleg* OR quadripleg* OR parapleg* OR spinal cord impaired OR spinal cord lesion)

Number of Studies	Total Duplicates Removed	Number of Excluded Studies Abstract + Title	Number of Excluded Studies at Full	Additional Articles Found	Total Included
MEDLINE: 62 EMBASE: 123 CINAHL: 16 Total: 191	-78 Total: 113	-63 Total: 50	-34 Total: 16	+1 Total: 17	17

Key Question 3: Risk Factors

MEDLINE/CINAHL/EMBASE (Human and English Applied)

(Spinal cord injur* or tetrapleg* or quadripleg* or parapleg* or spinal cord impaired or spinal cord lesion) AND (bone OR osteoporosis OR osteopenia OR mineral density OR mineral content OR BMD OR BMC OR bone mass OR bone turnover OR bone resorption OR bone composition) AND (epidemiology OR incidence OR prevalence OR frequency OR correlation OR risk factors OR odds ratio OR hazard ratio OR fracture OR fracture history) AND (demographic OR etiology OR race OR gender OR sex OR men OR women OR age OR duration OR level OR completeness OR severity OR AIS OR Frankel OR chronic OR acute OR spasticity OR activity OR ambulat* OR standing OR pharmacological agent OR medication OR BMI OR body weight OR body mass OR serum calcium OR calcium intake OR vitamin D OR biomarkers OR biochemical OR alcohol OR smoking)

Number of Studies	Total Duplicates Removed	Number of Excluded Studies Abstract + Title	Number of Excluded Studies at Full	Additional Articles Found	Total Included
MEDLINE: 963 EMBASE: 1610 CINAHL: 201 Total: 2774	-599 Total: 2175	-2114 Total: 61	-21 Total: 40	+15 Total: 55	55

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Key Question 5: Dual-Energy X-Ray Absorptiometry (DXA) Anatomical Sites

Medline/CINAHL/EMBASE (Human and English Applied)

(Dual-energy X-ray absorptiometry or DXA OR DEXA) AND (bone mineral* OR area* bone mineral* OR BMD OR aBMD OR BMC) AND (spinal cord injur* OR tetrapleg* OR quadripleg* OR parapleg* OR spinal cord impaired OR spinal cord lesion)

Number of Studies	Total Duplicates Removed	Number of Excluded Studies Abstract + Title	Number of Excluded Studies at Full	Additional Articles Found	Total Included
MEDLINE: 104 EMBASE: 227 CINAHL: 57 Total: 388	-135 Total: 253	-232 Total: 21	-12 Total: 9	+1 Total: 10	10

Key Questions 6 and 7: Interventions for Prevention and Treatment

MEDLINE/CINAHL/EMBASE (Human and English Applied)

(Dual-energy X-ray absorptiometry or DXA OR DEXA) AND (bone mineral* OR area* bone mineral* OR BMD OR aBMD OR BMC) AND (spinal cord injur* OR tetrapleg* OR quadripleg* OR parapleg* OR spinal cord impaired OR spinal cord lesion)

Number of Studies	Total Duplicates Removed	Number of Excluded Studies Abstract + Title	Number of Excluded Studies at Full	Additional Articles Found	Total Included
MEDLINE: 952 EMBASE: 2261 CINAHL: 274 Total: 3487	-725 Total: 2762	-2723 Total: 39	-14 Total: 25	+5 Total: 30	30

Key Question 9: Nutraceuticals and Supplements

Medline/CINAHL/EMBASE/PsycINFO (Human and English Applied)

(calcium OR vitamin D, OR Magnesium OR protein OR supplements OR nutraceuticals OR herbals OR curcumin OR nutrition) AND (bone mineral density OR areal bone mineral density OR bone mineral content OR BMD OR aBMD OR BMC) AND (spinal cord injur* OR tetrapleg* OR quadripleg* OR parapleg* OR spinal cord impaired OR spinal cord lesion)

Number of Studies	Total Duplicates Removed	Number of Excluded Studies Abstract + Title	Number of Excluded Studies at Full	Additional Articles Found	Total Included
MEDLINE: 57 EMBASE: 165 CINAHL: 19 PsycINFO: 28 Total: 269	-90 Total: 179	-155 Total: 24	-17 Total: 7	0 Total: 7	7

PubMed (Human and English Applied)

(Spinal cord injur* or tetrapleg* or quadripleg* or parapleg* or spinal cord impaired or spinal cord lesion) AND (bone OR osteoporosis OR osteopenia OR mineral density OR mineral content OR BMD OR BMC OR bone mass OR bone turnover OR bone resorption OR bone composition)

Number of Studies	Total Duplicates Removed	Number of Excluded Studies Abstract + Title	Number of Excluded Studies at Full	Additional Articles Found	Total Included
PubMed: 110 Total: 110	-6 Total: 104	-82 Total: 22	-11 Total: 11	0 Total: 11	11

Appendix C: Evidence Tables

Section 1.0 – Medical History, Fracture and Fall Risk Assessment

Evidence Table 1A: Risk Factors for Bone Loss in Acute and Chronic SCI

Author, Year Study Design Setting	Population Characteristics Sample Size Injury Level AIS Score Injury Etiology Mean Age Duration of Injury % Female Bone Characteristics Osteoporotic Status	Objective Comparison Groups	Timeline Data Source Clinical Risk Factors Examined	Risk Factors
				Non-Significant Risk Factors
Abderhalden, 2017 Retrospective Cohort Study USA	Fracture group N: 47 Level: 24 (51.1%) paraplegic, 21 (44.7%) tetraplegic, 2 (4.3%) missing; 18 (38.3%) complete, 26 (55.3%) incomplete, 3 (6.4%) missing AIS: 11 (23.4%) A, 3 (6.4%) B, 6 (12.8%) C, 10 (21.3%) D, 17 (36.2%) missing Etiology: 36 (76.6%) traumatic, 10 (21.3%) non-traumatic, 1 (2.1%) missing Age: mean 54.4 ± 12.3 years Duration: mean 18.3 ± 13.2 years % Female: 6.4% Hip BMD (g/cm²): 0.71 ± 0.19 Mean Hip T-score: -2.71 ± 1.49 Osteoporosis: 3 (6.4%) normal, 22 (46.8%) low bone density, 22 (46.8%) osteoporosis Non-Fracture group N: 505 Level: 282 (55.8%) paraplegic, 207 (41.0%) tetraplegic, 16 (3.2%) missing; 228 (45.2%) complete, 263 (52.1%) incomplete, 14 (2.8%) missing AIS: 176 (34.9%) A, 37 (7.3%) B, 48 (9.5%) C, 97 (19.2%) D, 147 (29.1%) missing Etiology: 402 (79.6%) traumatic, 88 (17.4%) non-traumatic, 15 (3.0%) missing Age: mean 52.2 ± 13.4 years Duration: mean 16.5 ± 13.3 years % Female: 9.1% Hip BMD (g/cm²): 0.79 ± 0.21 Mean Hip T-score: -2.24 ± 1.53 Osteoporosis Status: 94 (18.6%) normal, 188 (37.2%) low bone density, 223 (44.1%) osteoporosis	Objective: Identify whether DXA measurements predict osteoporotic fractures in SCI population. Comparing: demographic factors, injury characteristics and medicinal use of those who experienced a fracture during the study period vs. those who did not	Timeline: 2002 - 2012 Data Source: Demographic information was taken for individuals (≥ 2 years injury duration, ≥ 1 DXA measurement, not taking medication for osteoporosis) enrolled in the VA Spinal Cord Disorders Registry. Clinical examination using DXA (femoral neck, total hip) Clinical Risk Factors Examined: gender, age, race, etiology of SCI, SCI level, SCI completeness, AIS grade, SCI duration, Charlson comorbidity index, history of fractures, and medication use (proton pump inhibitors, glucocorticoids, mineralocorticoids, hydrochlorothiazide, thiazolidinediones, thyroid medications, anticonvulsants, opioids, benzodiazepines antidepressants [SSRI, SNRI, tricyclic])	Significant Risk Factors: 1. Individuals with normal aBMD likely to be (all p≤0.01): 2. Race: black a. Incomplete SCI b. AIS B-D 3. A lower hip T-Score predictive of incident fractures: a. Univariate: OR 0.75, 95%CI [0.61, 0.92] b. Multivariate: OR 0.73, 95%CI [0.57, 0.92] (covariates age, gender, race, SCI characteristics, comorbidities, medications) 4. Fracture history: Participants with fractures had lower hip T-scores than non-fracture participants (-2.71 ± 1.49 vs. -2.24 ± 1.53, p=0.05, respectively). Non-Significant Risk Factors: 1. Gender 2. Age 3. Etiology of SCI 4. SCI level 5. SCI duration Medication use (proton pump inhibitors, glucocorticoids, mineralocorticoids, hydrochlorothiazide, thiazolidinediones, thyroid medications, anticonvulsants, opioids, benzodiazepines antidepressants [SSRI, SNRI, tricyclic])

Bethel, 2016 Case-Control Study USA	Non-Fracture Group N: 19,151 Level: 43.2% paraplegic, 47.9% tetraplegic; 31.5% complete, 50.2% incomplete AIS: 14.9% A, 4.6% B, 5.8% C, 14.2% D Etiology: 60.7% traumatic, 18.6% non-traumatic Age: mean 56.2 ± 13.1 years Duration: mean 15.6 ± 14.3 years % Female: 3.3% BMD: __ Osteoporosis: __ Fracture Group N: 3,365 Level: 37.6% paraplegic, 55.2% tetraplegic; 42.2% complete, 45.2% incomplete AIS: 23.6% A, 4.9% B, 5.9% C, 12.2% D Etiology: 65.8% traumatic, 12.4% non-traumatic Age: Mean 54 ± 12.3 years Duration: Mean 18.4 ± 13.9 years % Female: 3.5% BMD: __ Osteoporosis: __	Objective: Identify risk factors for incidences of osteoporotic fractures over a 10-year period in individuals with chronic SCI. Comparing: demographic factors, injury characteristics and medicinal use of those who experienced a fracture during the study period vs. those who did not	Timeline: 2002 - 2012 Data Source: Demographic information was taken for all individuals in the VA Spinal Cord Dysfunction Registry, who had at least 2 years of documented SCI and was not taking medication for osteoporosis. Incidents of fractures during the study period were obtained from the Corporate Data Warehouse MedSAS datasets. Clinical Risk Factors Examined: gender, age, race, etiology of SCI, SCI level, SCI completeness, AIS grade, SCI duration, Charlson comorbidity index, fracture history, medication use (proton pump inhibitors, glucocorticoids, mineralocorticoids, hydrochlorothiazide, thiazolidinediones, thyroid medications, anticonvulsants, opioids, benzodiazepines antidepressants [SSRI, SNRI, tricyclic])	Significant Risk Factors Multivariate model - Adjusted for age, gender, race, etiology, level, extent and SCI duration. - Caucasian: HR 1.18; 95%CI (1.08-1.29) - Traumatic etiology of SCI: HR 1.16, 95%CI (1.04-1.30), in femur, tibia and fibula - Paraplegia: HR 1.09, 95%CI (1.02-1.18) - Complete SCI: HR 1.34, 95%CI (1.24-1.45) - SCI duration: HR 1.01 95%CI (1.01-1.01), in femur, tibia and fibula - Charlson Comorbidity Index: HR 1.12, 95%CI (1.10-1.14) - Anticonvulsants: HR 1.17, 95%CI (1.06-1.28) - Opioids use: HR 1.36, 95%CI (1.24-1.49) - History of hip fracture 1 year prior: HR 4.08, 95%CI (1.54-10.77) - History of non-hip fracture 1 year prior: HR 4.01, 95%CI (2.54-6.33) - Women aged ≥50 years: HR 1.56, 95%CI (1.18-2.06), compared with older men Non-Significant Risk Factors - Gender - Age Medication use: mineralocorticoids, glucocorticoid, hydrochlorothiazide, proton pump inhibitor, antidepressants (TCA, SNRI, and SSRI), thiazolidinediones, benzodiazepines, and thyroid medications
Biering-Sorensen, 1988 Cross-sectional Study Denmark	SCI N: 26 Level: C5-L4 AIS: __ Etiology: traumatic Age: range 20-65 years Duration: range 2-25 years % Female: 7.7% BMC (% of normative values): Femoral neck: 74.9 Femoral shaft: 73.4 Proximal tibia: 47.8 Osteoporosis: __ Controls Defined as healthy Male (20-85 years) baseline BMC (U cm-1):	Objective: To investigate the relationship between BMC and SCI level, spasticity and long leg braces usage. Comparing: Clinical characteristics within SCI group vs. BMC of healthy controls.	Timeline: unclear Data Source: Clinical examination using DPA (femoral neck, femoral shaft and proximal tibia), blood analysis. Clinical Risk Factors Examined: fracture history, spasticity, long leg brace usage, biomarkers (serum-Cr, ALP, calcium, phosphate)	Significant Risk Factors: - Fracture history: Significant difference in BMC (% of normal controls) between those with and without fracture history (n=4, mean 32.6%; n=8, mean 48.3%; p<0.05). - SCI level: Higher median femoral shaft BMC in thoracic vs. cervical lesion (80.7, 70.2-89.1 vs 64.0, 48.1-77.8; p<0.05) Non-Significant Risk Factors: - Spasticity - Long leg brace usage - Biomarkers - Cr - ALP - Calcium - Phosphate

	Femoral neck (n=47): 2.845 ± 0.389 Femoral shaft (n=42): 3.905 ± 0.437 Proximal tibia (n=22): 6.94 ± 1.12 Female (20-50 years) baseline BMC (U cm⁻¹): Femoral neck (n=51): $2,479 \pm 0.314$ Femoral shaft(n=51): 3.231 ± 0.293 Proximal tibia (n=26): 5.67 ± 0.85 Osteoporosis: __			
Carbone, 2013b (anticonvulsants) Cohort Study USA	Anticonvulsant users N: 5226 Level: 2834 paraplegia, 2392 tetraplegia; 1891 complete, 2143 incomplete, 1192 missing AIS: __ Etiology: traumatic Age: mean 57.14 ± 12.06 years Duration: mean 22.55 ± 13.53 years % Female: 0% Osteoporosis: __ Non-users N: 2221 Level: 1328 paraplegia, 893 tetraplegia; 833 complete, 889 incomplete, 499 missing AIS: __ Etiology: traumatic Age: mean 58.91 ± 13.85 years Duration: mean 24.04 ± 14.50 years % Female: 0% Osteoporosis: __ Lower Extremity Fractures (total population): 892 (7447)	Objective: To determine if there is an association between anticonvulsants use and lower extremity fracture in those with SCI. Comparing: Fracture association in anticonvulsants users vs non-users.	Timeline: 2002 - 2007 Data Source: Demographics and clinical status from Veterans Affairs Spinal Cord Dysfunction Registry Data and Veteran Affairs Medical Statistical Analysis System; thiazide usage obtained from Veterans Affairs pharmacy benefits management group prescription database. Clinical Risk Factors Examined: age, SCI duration, SCI level, Charlson comorbidity index, medications (anticonvulsants, heparin, opioids, osteoporosis therapies, thiazide diuretics, corticosteroid use, loop diuretics, proton pump inhibitors, SSRIs, thiazolidinediones, bisphosphonates)	Significant Risk Factors: - Significant factors for increased risk of fracture, multivariate analysis (covariates: age, race, SCI duration, SCI level, medication use): - Anticonvulsants: HR 1.17; 95%CI (1.01-1.36) - Alprazolam: HR 1.54; 95%CI (1.04-2.29) - Benzodiazepine: HR 1.28; 95%CI (1.11-1.47) - Diazepam: HR 1.23; 95%CI (1.06-1.41) - Temazepam: HR 1.28; 95%CI (1.01-1.62) - Anticonvulsant poly-therapy: HR 1.20; 95%CI (1.00-1.42) - Complete SCI: HR 1.69; 95%CI (1.45-1.98) - Heparin use: HR 1.28; 95%CI (1.02-1.61) - Opioid use: HR 1.78; 95%CI (1.54-2.06) - Osteoporosis drug therapies: HR 1.24; 95%CI (1.07-1.45) - Significant factors inversely associated to fracture, multivariate analysis: - Black race: HR 0.78; 95%CI (0.65-0.94) - Tetraplegia: HR 0.79; 95%CI (0.68-0.90) - Thiazide diuretic use: HR 0.74; 95%CI (0.59-0.93) - Diabetes: inversely associated with fracture, univariate analysis - With complications: HR 0.53; 95%CI (0.30-0.93) - Without complications: HR 0.75; 95%CI (0.61-0.92) Non-Significant Risk Factors: - Age - SCI duration - Seizures - Charlson comorbidity index - Duration of anticonvulsant use - Enzyme-inducing and non-enzyme-inducing anticonvulsants - Medications (corticosteroid use, loop diuretics, proton pump inhibitors, SSRIs, thiazolidinediones, bisphosphonates)
Carbone, 2013a (opioids) Retrospective Cohort Study	Opioid users N: 5106 Level: 2968 paraplegia, 2138 tetraplegia; 2158 incomplete, 1751 complete, 1197 unknown AIS: __ Etiology: traumatic	Objective: To determine if there is an association between opioid use and lower extremity fracture in those with	Timeline: September 2002 – October 2007 Data Source: Demographics and clinical status from Veterans Affairs Spinal Cord	Significant Risk Factors: - Opioid usage: - Positive relationship between opioids use and fractures (HR: 1.82; 95%CI [1.59–2.09]) after adjustment for covariates (age, race, SCI duration, SCI level, medications).

USA	Age: mean 57.18 ± 12.24 years Duration: 0-10 years: 1013 >10 years: 3397 Unknown: 696 % Female: 0% Osteoporosis: __ Lower Extremity Fractures: 597 over study duration Non-users N: 2341 Level: 1194 paraplegia, 1147 tetraplegia; 874 incomplete, 973 complete, 494 unknown AIS: __ Etiology: traumatic Age: mean 58.73 ± 13.43 years Duration: 0-10 years: 365 >10 years: 1663 Unknown: 313 % Female: 0% Osteoporosis: __ Lower Extremity Fractures: 295 over study duration	SCI. Comparing: Fracture association in opioid users vs non-users.	Dysfunction Registry Data and Veteran Affairs Medical Statistical Analysis System; opioid usage obtained from Veterans Affairs pharmacy benefits management group prescription database. Clinical Risk Factors Examined: opioid usage and duration of use, age, race, SCI duration and level, other medication use	b. Longer duration of use was significantly inversely related with fracture risk HR ≥6 months–1 year: HR 0.36; 95%CI [0.26–0.50] 1–2 years: HR 0.57; 95%CI [0.43–0.75] 2–3 years: HR 0.50; 95%CI [0.36–0.70] ≥3 years: HR 0.37; 95%CI [0.27–0.51] - Higher doses of codeine equivalents (>225 mg/day) were positively associated with fracture risk in adjusted models (p<0.0001). 2. In multivariate models, following factors were significantly associated with fractures (no data provided) - white race - paraplegia - complete injuries - longer SCI duration - receipt of osteoporosis therapies Non-Significant Risk Factors: - Age and opioid usage: No significant association between age (65± years) and opioid use on fractures. - Testosterone and opioid usage: No significant interaction between use of testosterone and opioids on fractures.
Carbone, 2014 Cohort Study USA Thiazides	Thiazide users N: 1433 Level: 1000 paraplegia, 433 tetraplegia; 487 complete, 611 incomplete, 355 missing AIS: __ Etiology: traumatic Age: mean 61.40 ± 10.9 years Duration: mean 26.10 ± 14.5 years % Female: 0% Lower Extremity Fractures: 110 (7.7%) over study duration Osteoporosis: __ Non-users N: 5536 Level: 2899 paraplegia, 2637 tetraplegia; 2053 complete, 2233 incomplete, 1250 missing AIS: __ Etiology: traumatic Age: Mean 56.60 ± 12.9 years Duration: Mean 22.10 ± 13.4 years % Female: 0% Lower Extremity Fractures: 722 (13%) over study duration Osteoporosis: __	Objective: To determine if there is an association between thiazide use and lower extremity fracture in those with SCI. Comparing: Fracture association in thiazide users vs non-users.	Timeline: 2002 to 2007 Data Source: Demographics and clinical status from Veterans Affairs Spinal Cord Dysfunction Registry Data and Veteran Affairs Medical Statistical Analysis System; thiazide usage obtained from Veteran Affairs Decision Support System pharmacy database. Clinical Risk Factors Examined: fracture history, SCI duration and level, race, history of seizures, Charlson comorbidity index medication and supplement use (thiazide diuretics, heparin, oral corticosteroids, loop diuretics, proton pump inhibitors, SSRIs, thiazidinolines, benzodiazepines, anticonvulsants, opioids, vitamin D, calcium)	Significant Risk Factors: - Significant factors for increased risk of fracture, multivariate analysis (covariates: age, race, SCI duration, SCI level, medication use): - Tetraplegia: HR 1.27; 95%CI (1.08-1.49), p<0.010 - Heparin: HR 1.46; 95%CI (1.12-1.89), p<0.010 - Benzodiazepines: HR 1.42; 95%CI (1.10-1.83), p<0.010 - Opioids: HR 1.82; 95%CI (1.55-2.14), p<.001 - Significant factors inversely associated to fracture, multivariate analysis: - Thiazide diuretics: HR 0.74; 95%CI (0.58-0.95), p=0.020 - Black race: HR 0.76; 95%CI (0.63-0.93), p=0.010 - Incomplete SCI: HR 0.57; 95%CI (0.48-0.68), p<0.001 - Significant combination therapies for decreased risk of fracture: - Thiazide and vitamin D supplementation: HR 0.43; 95%CI (0.22-0.85), p=0.02 Non-Significant Risk Factors: - Duration of thiazide use - History of seizures - Duration of SCI - Charlson comorbidity index Medications (oral corticosteroids, loop diuretics, proton pump inhibitors, SSRIs, thiazidinolines)

Chain, 2012 Cross-sectional Study Brazil	All N: 25 Level: C5-C7; tetraplegic Etiology: traumatic Age: mean 32 ± 9 years Active Group (>150 mins/week physical activity) N: 15 Level: 1 complete, 14 incomplete AIS: __ Age: mean 30 ± 9 years Duration: mean 8 ± 7 years % Female: 0% Mean Femoral neck aBMD (g/cm ²): 0.78 ± 0.16 years Mean Total femur aBMD (g/cm ²): 0.73 ± 0.16 Osteoporosis: __ Sedentary Group (No physical activity) N: 10 Level: 2 complete, 8 incomplete AIS: __ Age: mean 36 ± 11 years Duration: mean 15 ± 9 years % Female: 0% Mean Total femur aBMD (g/cm ²): 0.83 ± 0.18 Mean Femoral neck aBMD (g/cm ²): 0.79 ± 0.16 years Osteoporosis: __	Objective: Identify whether reported physical activity levels influence aBMD, bone metabolism and vitamin D status. Comparing: Clinical characteristics within active SCI group vs. sedentary SCI group.	Timeline: unclear Data Source: Clinical examination using DXA (femoral neck, total femur), blood analysis, self-reported physical activity. Clinical Risk Factors Examined: physical activity, age, BMI, SCI duration, serum calcium, calcium intake	Significant Risk Factors: 1. Physical Activity: Onset of physical activity post injury negatively correlated with aBMD, when controlled for body mass index and calcium intake. a. Femoral neck aBMD (r=-0.58, p<0.05) b. Femoral neck Z-score (r=-0.58, p<0.05) c. Total femur aBMD (r=-0.60, p<0.05) Non-Significant Risk Factors: 1. Level of activity a. Calcium intake
Changlai, 1996 Cross-sectional Study China	N: 157 Level: 108 C1-T10, 49 T11-L1; 117 complete, 40 incomplete AIS: __ Etiology: __ Age: range 20-70 years Duration: 84 ≤3 years, 73 >3 years % Female: 19.1% SCI severity Femoral neck BMD: Complete (n=117): 97 abnormal, 20 normal range Incomplete (n=40): 29 abnormal, 10 normal range SCI duration Femoral neck BMD: ≤3 years (n=84): 63 abnormal, 21 normal range >3 years (n=73): 63 abnormal, 10 normal range SCI level Femoral neck BMD: C1-T10 9 (n=108): 87 abnormal, 21 normal range T11-L1 (n=49): 39 abnormal, 10 normal range Osteoporosis: __	Objective: Determine the risk of fracture associated with SCI severity, SCI duration, and SCI level. Comparing: aBMD in comparison with clinical characteristics.	Timeline: unclear Data Source: Clinical examination using DPA (right femoral neck). Clinical Risk Factors Examined: SCI severity, SCI duration, SCI level	Significant Risk Factors: None reported Non-Significant Risk Factors: 1. SCI severity (complete vs. incomplete) 2. SCI duration (short duration [≤3 years] vs. long duration [>3 years]) 3. SCI level (high [C1-T10] vs. low [T11-L1])

Cirnigliaro, 2019 Cross-sectional Study USA	SCI < 1 year group (E-I) N: 19 Level: 12 paraplegic, 7 tetraplegic; 18 complete, 1 incomplete AIS: 12 A, 6 B, 1 C Etiology: traumatic Age: mean 36.6 ± 13.2 years Duration: mean 0.22 ± 0.15 years % Female: 31.6% Mean aBMD (g/cm2): Distal femur: 1.093 ± 0.176 Proximal tibia: 1.356 ± 0.210 Femoral neck: 1.068 ± 0.192 Total hip: 1.099 ± 0.181 Mean Z-score: Femoral neck: -0.05 ± 1.13 Total hip: -0.02 ± 1.01 Mean T-score: Femoral neck: 0.21 ± 1.37 Total hip: 0.73 ± 1.43 Osteoporosis: __ SCI 1-5 year group (E-II) N: 36 Level: 28 paraplegic, 8 tetraplegic; 18 complete, 18 incomplete AIS: 13 A, 5 B, 18 C Etiology: traumatic Age: mean 36.9 ± 11.9 years Duration: mean 3.1 ± 1.9 years % Female: 25% Mean aBMD (g/cm2): Distal femur: 0.886 ± 0.169 Proximal tibia: 1.084 ± 0.259 Femoral neck: 0.873 ± 0.141 Total hip: 0.826 ± 0.142 Mean Z-score: Femoral neck: -1.37 ± 1.01 Total hip: -1.76 ± 0.97 Mean T-score: Femoral neck: -1.30 ± 1.07 Total hip: -1.54 ± 1.18 Osteoporosis: __ SCI 6-10 year group (E-III) N: 19 Level: 11 paraplegic, 8 tetraplegic; 13 complete, 6 incomplete AIS: 7 A, 6 B, 6 C Etiology: traumatic Age: mean 40.1 ± 10.3 years Duration: mean 7.9 ± 1.4 years % Female: 15.8% Mean aBMD (g/cm2):	Objective: Examine the effect of SCI duration and rates of BMD decline in SCI participants. Comparing: Demographics within stratified groups based on SCI duration.	Timeline: unclear Data Source: Clinical examination using DXA (distal femur, proximal tibia, femoral neck, total hip). Clinical Risk Factors Examined: SCI duration, age, gender, SCI severity and level	Significant Risk Factors: - SCI duration: All aBMD sites decreased with SCI duration - Group comparisons - E-V vs. E-I, p<0.01 - E-V vs. E-II, p<0.01 - E-IV vs. E-I, p<0.01 - E-IV vs. E-II, p<0.01 - E-IV vs. E-III, p<0.01 - E-III vs. E-I, p<0.01 - Controls vs. E-V, p<0.01 - Controls vs. E-IV, p<0.01 - Controls vs. E-III, p<0.01 - Controls vs. E-II, p<0.01 - E-V vs. E-III, p<0.05 - E-IV vs. E-III, p<0.05 - Controls vs. E-II, p<0.05 - Individuals below Z-score and T-score thresholds, respectively. - E-I: 0% and 0% - E-II: 34% and 12% - E-III: 40% and 35% - E-IV: 81% and 35% - E-V: 87% and 60% - Controls: 0% and 0% Non-Significant Risk Factors: - Age - Gender - SCI severity - SCI level
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Distal femur: 0.838 ± 0.168 Proximal tibia: 0.958 ± 0.205 Femoral neck: 0.874 ± 0.179 Total hip: 0.827 ± 0.168 Mean Z-score: Femoral neck: -1.34 ± 1.64 Total hip: -1.78 ± 1.48 Mean T-score: Femoral neck: -1.27 ± 1.29 Total hip: -1.58 ± 1.29 Osteoporosis: __ SCI 11-20 year group (E-IV) N: 16 Level: 11 paraplegic, 5 tetraplegic; 15 complete, 1 incomplete AIS: 6 A, 9 B, 1 C Etiology: traumatic Age: mean 41.9 ± 11.9 years Duration: mean 15.4 ± 2.7 years % Female: 31.3% Mean aBMD (g/cm²): Distal femur: 0.714 ± 0.148 Proximal tibia: 0.781 ± 0.137 Femoral neck: 0.720 ± 0.089 Total hip: 0.662 ± 0.119 Mean Z-score: Femoral neck: -2.00 ± 1.40 Total hip: -2.55 ± 1.42 Mean T-score: Femoral neck: -2.44 ± 0.70 Total hip: -2.88 ± 0.82 Osteoporosis: __ SCI >20 year group (E-V) N: 15 Level: 6 paraplegic, 9 tetraplegic; 10 complete, 5 incomplete AIS: 8 A, 2 B, 5 C Etiology: Traumatic Age: mean 50.1 ± 5.6 years Duration: mean 31 ± 6.0 years % Female: 20% Mean aBMD (g/cm²): Distal femur: 0.649 ± 0.136 Proximal tibia: 0.788 ± 0.197 Femoral neck: 0.716 ± 0.131 Total hip: 0.662 ± 0.125 Mean Z-score: Femoral neck: -2.00 ± 0.88 Total hip: -2.67 ± 0.82 Mean T-score: Femoral neck: -2.39 ± 0.89 Total hip: -2.90 ± 0.90 Osteoporosis: __			
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	Control group Controls defined as healthy, able-bodied. N: 17 Age: mean 36.0 ± 12.5 years % Female: 11.8% Mean aBMD (g/cm²): Distal femur: 1.037 ± 0.203 Proximal tibia: 1.320 ± 0.249 Femoral neck: 1.075 ± 0.120 Total hip: 1.023 ± 0.131 Mean Z-score: Femoral neck: 0.17 ± 0.82 Total hip: -0.02 ± 0.73 Mean T-score: Femoral neck: 0.19 ± 0.87 Total hip: 0.29 ± 0.85 Osteoporosis: __			
Dauty, 2000 Cross-sectional Study France	SCI group N: 31 Level: 20 paraplegic, 11 tetraplegic; 26 complete, 5 incomplete AIS: 22 A, 4 B, 3 C, 2 D Etiology: traumatic Age: mean 36 ± 12.3 years (SCI and control group) Duration: mean 6 years, 6 months to 19 years % Female: 0% BMD: __ Osteoporosis: __ Fracture History: 1 high energy and 8 fragility fractures (2 at femoral neck, 3 in supracondylar area, and 1 in diaphyseal area) Controls Controls defined as healthy, gender and age matched, presenting with sedentary daily life. N: 31 Age: mean 36 ± 12.3 years (combined SCI and control group) % Female: 0% BMD: __ Osteoporosis: __	Objective: To investigate aBMD and BMC in relation to SCI duration, daily standing and use of long leg braces. Comparing: Clinical characteristics in SCI group vs. controls; passive standing vs. non-passive standing; long leg brace usage (n=6) vs. non-long leg brace usage.	Timeline: unclear Data Source: Clinical examination using DXA (aBMD [femoral neck, trochanter] and BMC [lower 1/3 distal femur, upper 1/3 proximal tibia] and blood analysis. Clinical Risk Factors Examined: SCI duration, SCI level, passive standing (with and without long leg braces), duration of initial bed rest, blood analysis (unclear if investigated in relation to clinical risk factors)	Significant Risk Factors: 1. SCI duration: Correlated to a decrease in BMC at upper 1/3 of tibia ($r^2=0.2561$, $p=0.02$) 2. Duration of initial bedrest: Correlated to decreased aBMD at trochanter ($r^2=0.2215$, $p=0.009$) Non-Significant Risk Factors: 1. SCI level 2. Use of long leg braces Daily passive standing
Demirel, 1998 Cross-sectional Study Turkey	N: 41 Level: 5 C4-C7, 6 T1-T6, 20 T7-T12, 10 L1-L3; 36 paraplegic, 5 tetraplegic; 21 complete, 20 incomplete AIS: __ Etiology: 38 traumatic, 3 non-traumatic Age: mean 35.8 ± 12.7 years Duration: mean 9.5 ± 4.5 years months % Female: 22% Mean Z-score: Males (site not reported): -2.6 ± 1.48 Females (site not reported): -2.13 ± 1.89	Objective: To evaluate correlations between BMD and SCI level, SCI duration, spasticity and blood analysis. Comparing: Clinical characteristics within SCI group.	Timeline: August 1995 – February 1996 Data Source: Clinical examination using DXA (whole-body composition at 7 sites, used values from arms and legs [sites not reported]) and blood analysis (serum calcium, phosphorus, ALP). Clinical Risk Factors	Significant Risk Factors: 1. SCI duration: a. Paraplegia duration: Strong correlation with lower extremity Z-score ($r=-0.80$, $p<0.001$) b. Tetraplegia duration: Moderate correlation with Z-scores in lower extremities ($r=-0.42$, $p=0.005$) c. SCI duration correlated to ALP levels in pooled patient group ($r=0.48$, $p=0.001$) 2. SCI level: Osteopenia more apparent in complete SCI than incomplete Z-scores (-2.29 ± 0.51 vs. -0.12 ± 0.22, $p<0.05$). 3. Spasticity: Higher Z-scores in patients with spasticity

	Paraplegia lower extremity: -2.19 ± 3.5 Tetraplegia lower extremity: -2.50 ± 0.55 Osteoporosis: __		Examined: age, gender, SCI duration, SCI level, spasticity, blood analysis	than flaccid patients (0.078 ± 0.62 vs. -0.118 ± 0.46, $p < 0.05$). Non-Significant Risk Factors: - Age - Gender - Biomarkers - ALP levels - Serum calcium - Phosphorus
Dionyssiotis, 2008 Cross-sectional Study Greece	All SCI N: 31 Level: paraplegic; complete AIS: 31 A Etiology: __ Age: mean 39.2 ± 15 years % Female: 0% Leg aBMD (g/cm²): mean 0.97 ± 0.1 Osteoporosis: __ High Level SCI Group N: 16 Level: T4-T7 Age: mean 35 ± 14 years Duration: mean 5.97 ± 5.9 years BMD: __ Low Level SCI Group N: 15 Level: T8-T12 Age: mean 39 ± 14 years Duration: mean 5.65 ± 5.8 years BMD: __ Control group Controls defined as healthy, able-bodied N: 33 Age: mean 36.9 ± 19 years % Female: 0% Leg aBMD (g/cm²): mean 1.22 ± 0.08 Inconsistency with some values reported in tables and in text (mean age, leg aBMD)	Objective: To describe aBMD differences in relation to SCI duration and SCI level. Comparing: SCI group vs controls; high level group vs. low level group	Timeline: unclear Data Source: Clinical examination using DXA (leg aBMD, site not reported). Clinical Risk Factors Examined: SCI duration, SCI level	Significant Risk Factors: - SCI duration and SCI level: - Paraplegic leg aBMD negatively correlated with SCI duration ($r = -0.46$, $p = 0.009$) - Stronger correlation between SCI duration and high level paraplegic leg aBMD ($r = -0.73$, $p = 0.001$) than in low level paraplegic leg aBMD ($r = -0.14$, $p = 0.617$). Non-Significant Risk Factors: - SCI duration in low paraplegia
Dionyssiotis, 2009 Cross-sectional Study Greece	All SCI N: 30 Level: paraplegic; complete AIS: __ Etiology: __ Osteoporosis: __ High Level SCI group N: 15	Objective: To investigate lower-limb BMC in relation to SCI level and SCI duration. Comparing: Clinical parameters within high level group vs.	Timeline: unclear Data Source: Clinical examination using pQCT (stress-strain index at 14% and 38% tibia), DXA (lower limb BMC). Clinical Risk Factors	Significant Risk Factors: - SCI duration: - All SCI participants: SCI duration correlation with lower limb BMC ($r = -0.460$, $p = 0.009$); correlation with SSI at 14% tibia ($r = -0.423$, $p = 0.008$). - High level participants: SCI duration correlation with high level group lower limb BMC ($r = -0.658$, $p = 0.01$); correlation with stress-strain index at 38% tibia in high level group ($r = -0.475$, $p = 0.040$).

	Level: T4-T7 Age: mean 32.88 ± 15.6 years Duration: mean 5.97 ± 5.9 years % Female: 0% Mean Lower Limb BMC (g): 898.14 ± 202.88 High Level SCI group N: 15	low level group vs. control group.	Examined: SCI duration, SCI level, spasticity	c. Low level: Correlation with stress-strain index at 14% tibia in low level group ($r=-0.473$, $p=0.041$); correlation with difference between stress-strain index at 38% tibia and 14% tibia ($r=-0.534$, $p=0.027$) Non-Significant Risk Factors: 1. Spasticity
Doherty, 2014 Cross-sectional Study USA	Walking Group N: 54 Level: 2 complete, 52 incomplete AIS: 2 A/B, 52 C/D Etiology: __ Age: mean 62.6 ± 12.0 years Duration: mean 22.1 ± 13.2 years % Female: 0% Mean aBMD (g/cm²): Distal femur: 0.91 ± 0.18 Proximal tibia: 1.02 ± 0.21 Total hip: 0.99 ± 0.19 Femur neck: 0.93 ± 0.15 Osteoporosis: 8 osteoporotic, 19 osteopenic, 26 normal, 1 missing Wheelchair group N: 95 Level: 74 complete, 21 incomplete AIS: 74 A/B, 21 C/D Etiology: __ Age: mean 51.3 ± 12.5 years Duration: years 21.1 ± 11.8 years % Female: 0% Mean aBMD (g/cm²): Distal femur: 0.64 ± 0.19 Proximal tibia: 0.63 ± 0.22 Total hip: 0.73 ± 0.20 Femur neck: 0.75 ± 0.20 Osteoporosis: 67 osteoporotic, 9 osteopenic, 12 normal, 7 missing	Objective: Investigate the association between adiponectin or leptin and BMD in SCI participants that are wheelchair bound or have the ability to walk. Comparing: Walking group (patients with the ability to walk) vs. wheelchair group	Timeline: unclear Data Source: Clinical examination using DXA (distal femur, proximal tibia, total hip, femur neck), blood analysis, physical exam. Clinical Risk Factors Examined: ambulatory status, age, SCI duration, total fat mass, BMI body weight, biomarkers (adiponectin, CTx, OC, leptin),	Significant Risk Factors: 1. Walking group: a. aBMD positively associated with: b. Body weight, $p=0.01$ c. BMI, $p=0.03$ d. Lean mass, $p=0.0008$ 2. Wheelchair group a. Lean mass: Positively associated with aBMD, $p=0.03$. b. CTx and OC: Negatively associated with aBMD, $p=0.01$ and $p=0.02$, respectively. c. Adiponectin: Negatively associated with aBMD before and after adjusting for lean mass, $p=0.0005$ and $p=0.004$, respectively; significant inverse linear trend with aBMD, $p=0.002$. Non-Significant Risk Factors: 1. Walking group a. Age b. SCI duration c. Vitamin D level d. Total fat mass e. CTx f. OC g. Adiponectin h. Adiponectin and fracture history or SCI duration i. Leptin 2. Wheelchair group a. Body weight b. BMI c. Leptin d. Adiponectin and fracture history or SCI duration
Doubelt, 2015 Cross-sectional Study Canada	SCI N: 34 Level: C1-T11; 12 paraplegic, 22 tetraplegic; 17 complete, 17 incomplete AIS: 13 A, 4 B, 16 C, 1 D Etiology: 27 traumatic, 7 non-traumatic Age: mean 40.0 ± 10.9 years Duration: mean 12.7 ± 9.9 years % Female: 5.8% Mean Femoral neck aBMD (g/cm²) (n=28): 0.69 ± 0.19 Mean Femoral neck Z-score (n = 23): -1.49	Objective: To investigate the association between femoral neck aBMD, obesity and nutrition. Comparing: aBMD, obesity and blood analysis within SCI participants.	Timeline: March 2011 – April 2013 Data Source: Clinical examination using DXA (femoral neck), demographics and medical history from interview, blood analysis. Clinical Risk Factors	Significant Risk Factors: 1. Visceral adipose tissue: Moderate correlation with femoral neck aBMD ($r=0.444$, 95%CI [0.00–0.02], $p=0.018$) 2. Blood analysis: a. Leptin: Correlation with femoral neck aBMD ($r=0.529$, 95%CI [0.00–0.02], $p=0.005$) b. Insulin: Correlation with femoral neck aBMD ($r=0.544$, 95%CI [0.00–0.00], $p=0.003$) Non-Significant Risk Factors: 1. Blood analysis

	Mean Femoral neck T-score (n = 5): -1.04 Osteoporosis: 4% osteoporotic, 11% osteopenic Controls Described as non-SCI controls. N: 8 Mean Femoral neck aBMD (g/cm²) (n=8): 0.92 ± 0.12 Mean Femoral neck Z-score (n = 6): 0.68 Mean Femoral neck T-score (n = 2): -0.9		Examined: visceral adipose tissue, blood analysis (25[OH]D, adiponectin, leptin, insulin, calcium intake)	a. Calcium intake b. 25(OH)D 2. Adiponectin
Eser, 2004 Cross-sectional Study Germany	SCI N: 89 Level: 80 C5–T12 (spastic) and 9 L1–L3 (flaccid); 65 paraplegic, 24 tetraplegic AIS: __ Etiology: traumatic Age: mean 41.5 ± 14.2 years Duration: mean 12.0 ± 11.3 years % Female: 0% 4% Femur (Mean, SD) CSAtot: 4010 ± 365 mm² vBMDtot: 146.5 ± 29.1 mg/cm³ vBMDtrab: 112.8 ± 28.3 mg/cm³ 4% Tibia (Mean, SD) CSAtot: 1324 ± 192 mm² vBMDtot: 135.0 ± 26.9 mg/cm³ vBMDtrab: 66.1 ± 23.4 mg/cm³ 38% Tibia (Mean, SD) Cortical CSA: 249.3 ± 59.3 mm² CSAtot: 464.8 ± 66.1 mm² vBMDcort: 1125.9 ± 52.6 mg/cm³ Osteoporosis: __	Objective: Describe bone loss of trabecular and cortical bone, and bone geometry in relation to SCI duration. Comparing: Differences between bone parameters and SCI duration in SCI participants.	Timeline: 4 month study duration. Data Source: Clinical examination using pQCT (4% femur, 4% tibia, 38% tibia). Clinical Risk Factors Examined: SCI duration	Significant Risk Factors: - SCI duration: Total vBMD and trabecular vBMD decreased with SCI duration. - Femur - Total vBMD: R²=0.67 - Trabecular vBMD: R²=0.65 - Tibia - Total vBMD: R²=0.7 - Trabecular vBMD: R²=0.72 Non-Significant Risk Factors: - None reported
Eser, 2005 Cross-sectional Study Switzerland	N: 54 Level: 48 C5–T12 (spastic), 6 L1–L3 (flaccid); 47 paraplegia, 7 tetraplegia AIS: A/B Etiology: traumatic Age: range 24–72 years, no mean reported Duration: range 5–48.5 years, no mean reported % Female: 9.3% BMD: __ Osteoporosis: __	Objective: To investigate the relationships between spasticity, lifestyle factors and BMD in participants with SCI. Comparing: Clinical and demographic characteristics within SCI group.	Timeline: unclear Data Source: Clinical examination using pQCT (4%, 25% femur; 4%, 38%, 66% tibia), spasticity test and questionnaire. Clinical Risk Factors Examined: age, spasticity, sitting hours, smoking status, weight, SCI level, medications	Significant Risk Factors: - Lesion level: Correlated to 4% femur vBMDtrab (r=0.34, p=0.008) - Weight and sports before injury: Correlated with tibial normalized CSA (r=0.35, p=0.006) - Spasticity: Correlation with femur parameters - vBMDtot (4% femur; n=48): r=0.384, p=0.005 - vBMDtrab (4% femur; n=48): r=0.352, p=0.008 - vBMDcort (25% femur, n=41): r=0.0364, p=0.01 - Normalized (height) cortical thickness (25% femur; n=48): r=0.332, p=0.01 - Normalized (height) cortical CSA (25% femur, n=48): r=0.33, p=0.01 - Weight: - Correlation with femoral normalized total cross-sectional area (r=0.328, p=0.01) - Negative correlation with tibial dyaphysis BMDcortical (r=-0.3, p=0.01) - Daily hours spent sitting: Correlation with 25% femur vBMDcort (r=0.44, p=0.003)

				6. Post injury smoking: - Correlation with 25% femur vBMDcort ($r=0.33$, $p=0.02$) - Correlation with tibial diaphysis vBMDcort ($r=0.32$, $p=0.01$) 7. Age: Negatively correlated to 4% tibia cortical CSA ($r=-0.3$, $p=0.02$) Non-Significant Risk Factors: - Bisphosphonate useage - Calcium intake
Frey-Rindova, 2000 Prospective Longitudinal Study Switzerland	N: 27 Level: 9 cervical, 17 thoracic, 1 lumbar AIS: Frankel: 10 A, 10 B, 7 C Etiology: traumatic Age: mean 36.9 ± 13.7 years Duration: acute % Female: 6.9% Mean BMDtrab (g/cm ³): All subjects (n=24): 310 ± 67 Paraplegic (n=16): 314 ± 70 Tetraplegic (n=6): 299 ± 64 Active (n=13): 316 ± 72 Inactive (n=11): 302 ± 64 Mean BMDcort (g/cm ³): All subjects (n=24): 924 ± 129 Paraplegic (n=18): 936 ± 136 Tetraplegic (n=6): 893 ± 113 Active (n=13): 935 ± 136 Inactive (n=11): 910 ± 126 Osteoporosis: __	Objective: Investigate the factors involved with the decrease of trabecular and cortical BMD in SCI participants. Comparing: Clinical characteristics within SCI group.	Timeline: 1, 6, 12 months post-SCI Data Source: Clinical examination using pQCT (tibia) and physical examination. Clinical Risk Factors Examined: SCI duration, SCI level, spasticity, physical activity	Significant Risk Factors: - SCI duration: Significant decrease in bone parameters at 12 months post-SCI - Tibia BMDtrab (g/cm³): - All participants: 262 ± 65, $p<0.05$ - Paraplegic: 261 ± 63, $p<0.05$ - Tetraplegic: 265 ± 74, $p<0.05$ - Active: 277 ± 47, $p<0.05$ - Inactive: 249 ± 78, $p<0.05$ - Tibia BMDcort (g/cm³): - All participants: 855 ± 114, $p<0.01$ - Paraplegic: 876 ± 120, $p<0.01$ - Tetraplegic: 811 ± 95, $p<0.01$ - Active: 889 ± 116, $p<0.01$ - Inactive: 827 ± 112, $p<0.01$ Non-Significant Risk Factors: - SCI level: paraplegic vs. tetraplegic - Spasticity - Physical Activity
Garland, 2001a Cross-sectional Study USA	N: 144* Level: 57 complete paraplegic, 25 incomplete paraplegic, 37 complete tetraplegic, 25 incomplete tetraplegic AIS: __ Etiology: __ Age: mean 39.4 ± 10.8 years Duration: mean 12.7 ± 8.8 years % Female: 10% BMD: __ Osteoporosis: __	Objective: Investigate contributions of age, SCI duration, SCI level on aBMD of the hip and knee. Comparing: clinical characteristics within groups; complete vs. incomplete; paraplegic vs. tetraplegic.	Timeline: unclear Data Source: Clinical examination using DXA (hip [Ward's triangle], knee [distal femur, proximal tibia]). Clinical Risk Factors Examined: age, SCI duration, SCI level, BMI	Significant Risk Factors: - SCI duration: Weak, significant correlation between SCI duration and knee aBMD ($r=0.17$, $p=0.023$), decline of knee BMD with duration in each SCI level. - SCI level - Incomplete injuries had higher knee aBMD than those with complete injuries ($p<0.05$). - Significant aBMD difference at the hip between SCI levels ($p<0.0001$). - Complete tetraplegia averaged ~2 SD below hip Z-score norm (when adjusted for age, gender, and race). - Incomplete tetraplegia and complete paraplegia averaged ~1 SD below hip Z-score norm (when adjusted for age, gender, and race). - BMI: - Significantly associated with knee aBMD ($r=0.37$, $p<0.0001$). - Significantly associated with hip Z-score ($r=0.23$, $p=0.003$).

				4. Age: Significantly associated with hip aBMD ($r=0.23$, $p=0.003$). Negative linear relationship between hip aBMD and age. Non-Significant Risk Factors: 1. BMI: Relationship with hip aBMD approached significance ($p=0.052$). 2. Age: Nonsignificant relationship between hip Z-score
Garland, 2001 Cross-sectional Study USA	All SCI N: 31 (n=6 group I, n=16 group II, n=9 group III) Level: C-T; complete AIS: __ Etiology: __ % Female: 100% Osteoporosis: __ SCI group I (≤ 30 years old) N: 6 Age: mean 25.7 ± 4.2 years Duration: mean 5.7 ± 2.3 years Mean aBMD (g/cm²): Ward's triangle: 0.65 ± 0.15 Distal Femur: 0.58 ± 0.11 Mean Ward's triangle Z-score: -1.13 SCI group II (31-50 years old) N: 16 Age: mean 41.2 ± 6.2 years Duration: mean 16.1 ± 9.4 years Mean aBMD (g/cm²): Ward's triangle: 0.52 ± 0.11 Distal Femur: 0.52 ± 0.13 Mean Ward's triangle Z-score: -1.33 SCI group III (>50 years old) N: 9 Age: mean 64.9 ± 7.9 years Duration: mean 28.9 ± 11.4 years Mean aBMD (g/cm²): Ward's triangle: 0.39 ± 0.18 Distal Femur: 0.45 ± 0.12 Mean Ward's triangle Z-score: -1.14 All Controls (able bodied) N: 17 (n=5 group I, n=7 group II, n=5 group III) Age: Group I mean 27.4 ± 1.7 years Group II mean 47.4 ± 2.4 years Group III mean 59.4 ± 2.7 years % Female: 100% Mean Ward's triangle aBMD (g/cm²):	Objective: Investigate changes to aBMD with association to age, body weight, and SCI duration in female SCI participants. Comparing: age ≤ 30 years SCI group (group I) vs. age 31-50 years SCI group (group II) vs. age >50 years SCI group (group III) vs. controls	Timeline: unclear Data Source: Clinical examination using DXA (Ward's triangle and distal femur). Clinical Risk Factors Examined: age, SCI duration, body weight	Significant Risk Factors: 1. Duration of injury: a. Moderate correlation of distal femur aBMD with SCI duration ($r=-0.32$, $p=0.037$). b. Significant correlation of Ward's triangle aBMD and SCI duration ($r=-0.36$, $p=0.025$). 2. Age: a. Modest negative correlation between distal femur aBMD and age ($r=-0.34$, $p=0.032$). b. Negative correlation between Ward's triangle aBMD and age ($r=-0.58$, $p=0.001$). Non-Significant Risk Factors: Body weight

	Group I: 0.80 ± 0.09 Group II: 0.74 ± 0.25 Group III: 0.51 ± 0.14 Mean distal femur aBMD (g/cm²): Group I: 0.95 ± 0.18 Group II: 0.93 ± 0.18 Group III: 0.83 ± 0.09 Mean Ward's triangle Z-score: Group I: 0.33 Group II: 1.01 Group III: -0.42 Osteoporosis: __			
Garland, 2004 Cross-sectional Study USA	N: 152 Level: 82 paraplegia, 70 tetraplegia; 102 complete, 50 incomplete AIS: __ Etiology: __ Age: mean 38.8 ± 11.5 years Duration: mean 12.9 ± 9.3 years % Female: 14.5% BMD: __ Osteoporotic Status: 77 osteoporotic (8 fractures), 75 normative (1 fracture) Fracture History: 8 fractures in osteoporotic group, 1 fracture in normative group	Objective: To investigate modifiable and non-modifiable risk factors for bone loss. Comparing: BMD in relation to age, SCI duration, SCI level, and lifestyle habits.	Timeline: unclear Data Source: Clinical examination using DXA (distal femur, proximal tibia), lifestyle questionnaire. Clinical Risk Factors Examined: SCI level, BMI, age, lifestyle factors	Significant Risk Factors: 1. Complete SCI: $p < 0.0001$; from OR analysis, 617% more likely to have BMD in osteoporotic category. 2. BMI: $p = 0.0035$; from OR analysis, every BMI unit increase lowered odds of being in osteoporotic category by 11.29%. 3. Age: $p = 0.0394$; from OR analysis, each year increase in age increased odds of being in osteoporotic category by 3.54%. Non-Significant Risk Factors: Alcohol use
Garland, 2008 Longitudinal Study USA	N: 31 Level: 16 paraplegic, 15 tetraplegic (0% women); complete AIS: __ Etiology: __ Age: mean 39.7 ± 10.6 years Duration: mean 14.6 ± 8.7 years % Female: 13% Mean aBMD (g/cm²): Hip: 0.48 ± 0.21 Distal femur: 0.41 ± 0.12 Knee: 0.55 ± 0.12 Proximal tibia: 0.54 ± 0.14 Mean hip Z-score: -1.9 Osteoporosis: __	Objective: Investigate longitudinal aBMD and demographics in SCI participants. Comparing: baseline vs. post-, non-intervention	Timeline: baseline and follow up at 5 years (5.06 ± 0.9 years) Data Source: Clinical examination using DXA (knee [distal femur and proximal tibia]). Clinical Risk Factors Examined: gender (paraplegia), SCI duration, SCI level	Significant Risk Factors: 1. Tetraplegia: Lower aBMD ($p < 0.0001$); significantly lower hip Z-scores than those with paraplegia; larger decrease in aBMD from baseline to post-examinations vs. paraplegic participants ($p < 0.0001$). 2. Gender*: Females had lower hip and knee aBMD ($p = 0.002$); significant differences in hip Z-score (female Mean baseline -1.1, post- -0.9; men Mean baseline -1.3, post- -0.6). <i>*small sample female sample size, only comparing paraplegics</i> Non-Significant Risk Factors: None reported
Gaspar, 2012 Cross-sectional Study Brazil	SCI group N: 25 Level: T2-T12, paraplegic; complete AIS: A/B Etiology: __ Age: mean 30.8 ± 6.6 years Duration: mean 68.4 ± 65.4 months % Female: 0% Mean aBMD (g/cm²): Femoral neck: 0.73 ± 0.12 Distal femur: 0.88 ± 0.17 Total femur: 0.77 ± 0.13	Objective: Evaluate relationship between aBMD, body composition, and fracture incidence. Comparing: Clinical characteristics in SCI group vs. controls.	Timeline: unclear Data Source: Clinical examination using DXA (femoral neck, distal femur, total femur). Clinical Risk Factors Examined: SCI duration, standing status, total mass	Significant Risk Factors: 1. SCI duration: Displayed an inverse relationship with distal femur aBMD ($r = -0.38$, $p = 0.05$). Non-Significant Risk Factors: 1. Ambulatory status: standing vs. non-standing 2. Total mass

	Osteoporosis: __ Control group (able-body, age-matched) N: 17 Age: mean 31.9 ± 5.6 years % Female: 0% Mean aBMD (g/cm2): Femoral neck: 0.96 ± 0.14 Distal femur: 1.25 ± 0.19 Total femur: 1.06 ± 0.15 Osteoporosis: __			
Gifre, 2014 Retrospective Cohort/Case control study Spain	All SCI N: 63 Level: 34 (54%) AIS: 34A, 9B, 17C, 3D Etiology: traumatic Age: mean 36 ± 20 years Duration: mean 8 ± 8 weeks post SCI % Female: 20.6% BMD: __ Osteoporosis: __ Participants with Fractures N: 10 Level: 8 paraplegics, 2 tetraplegics; 2 cervical, 7 thoracic, 1 lumbar AIS: 8 A Etiology: Age: mean 34 ± 16 years % Female: 0% BMD: __ Participants without Fractures N: 53 participants Level: 32 paraplegics, 21 tetraplegics; 20 cervical, 28 thoracic, 5 lumbar AIS: 26 A Age: mean 37 ± 21 years % Female: 24.5% BMD: __	Objective: To analyze the incidence and factors related to the development fractures in patients with traumatic SCI. Comparing: Participants with traumatic SCI with and without fractures.	Timeline: January - December 2000, follow-up of patient records to 10 years (retrospectively) Data Source: Medical records from Guttman Neurorehabilitation Institute Clinical Risk Factors Examined: Fracture incidence (10 years following SCI), SCI level and severity, spasticity, standing activity, fracture history.	Significant Risk Factors: 1. Complete (AIS A): fracture incidence RR 4.043, 95%CI (1.081–23.846), p=0.037 Non-Significant Risk Factors: 1. Gender 2. Age 3. Paraplegia/tetraplegia 4. Spasticity 5. Level of lesion 6. Tobacco consumption 7. Alcohol consumption 8. Manual or electrical wheelchair 9. Weight-bearing standing 10. Sports activities 11. Comorbidities
Gifre, 2015 Prospective observational study Spain	All N: 35 Level: 51% paraplegic, 49% tetraplegic AIS: 33 A, 2 B Etiology: traumatic Age: mean 35 ± 16 years Duration: mean 100 ± 35 days % Female: 3% Mean femoral neck aBMD (g/cm2): 1.045 ± 0.159 Mean total femur aBMD (g/cm2): 1.053 ± 0.161	Objective: To analyze the risk factors, including clinical, densitometric, and biochemical factors, related to the development of osteoporosis in patients with recent complete SCI.	Timeline: June 2010 to December 2013; baseline, 6 month and 12 month follow-up Data Source: clinical examination using DXA (femoral neck and total femur) and blood analysis. Clinical Risk Factors	Significant Risk Factors: 1. P1NP: Osteoporosis group had higher P1NP than non-osteoporosis group (188 ± 89 vs. 135 ± 87 ng/mL, p=0.039, respectively); RR 3.08; 95%CI (1.10-8.57), p=0.017; good diagnostic ability (AUC 0.75, 95%CI [0.54-0.95]) 2. BALP: Osteoporosis group had higher BALP than non-osteoporosis group (14.2 ± 3.91 vs. 11.5 ± 2.29 ng/mL, p=0.024, respectively); RR 2.40; 95%CI (1.10-5.23), p=0.041; good diagnostic ability (AUC 0.77, 95%CI [0.57-0.96])

	Osteoporosis group N: 13 Level: 46% paraplegic, 54% tetraplegic AIS: 12 A, 1 B Etiology: traumatic Age: mean 40 ± 17 years Duration: mean 100 ± 28 days % Female: 0% Mean femoral neck aBMD (g/cm²): 0.940 ± 0.130 Mean total femur aBMD (g/cm²): 0.940 ± 0.090 Non-Osteoporosis group N: 12 Level: 42% paraplegic, 58% tetraplegic AIS: 13 A Etiology: traumatic Age: mean 34 ± 18 years Duration: mean 100 ± 28 days % Female: 0% Mean femoral neck aBMD (g/cm²): 1.16 ± 0.150 Mean total femur aBMD (g/cm²): 1.190 ± 0.140	Comparing: Clinical and demographic characteristics in relation to osteoporosis status in the 12 months after SCI.	Examined: age, gender, BMI, toxic habits, level, SCI severity and level, SCI duration, biomarkers (P1NP, BALP, and CTx, 25[OH]D)	Non-Significant Risk Factors: 1. SCI duration 2. SCI level: paraplegic vs. tetraplegic 3. Age 4. BMI 5. Spastic/flaccid 6. PTH 7. 25(OH)D 8. CTx
Goktepe, 2004 Cross-sectional Study Turkey	Wheelchair basketball group N: 17 Level: 2 T1-T6, 12 T6-T12, 3 lumbosacral AIS: 12 A, 1 B, 4 C Etiology: traumatic Age: mean 28.4 ± 6.4 years Duration: mean 6.3 ± 2.8 years % Female: 0% Mean aBMD (g/cm²): Femoral neck: 0.82 ± 0.17 Ward's triangle: 0.80 ± 0.21 Trochanter: 0.65 ± 0.12 Total Femur: 0.79 ± 0.12 Mean T-Score: Femoral neck: -1.89 ± 1.37 Ward's triangle: -1.17 ± 1.66 Trochanter: -2.34 ± 1.01 Total Femur: -2.25 ± 0.94 Osteoporosis: __ Control group Defined as chronic paraplegic participants, age and SCI duration matched. N: 17 Level: 4 T1-T6, 9 T6-T12, 4 lumbosacral AIS: 13 A, 4 C Etiology: traumatic Age: mean 28.5 ± 3.5 years Duration: mean 6.1 ± 2.2 years % Female: 0%	Objective: Investigate the effect of activity on BMD in wheelchair basketball players vs. sedentary control group. Comparing: Activity levels within wheelchair basketball players (3, 2-hour exercise sessions per week) vs. matched control group.	Timeline: unclear Data Source: Clinical examination using DXA (femoral neck, Ward's triangle, trochanter, total femur). Clinical Risk Factors Examined: activity levels	Significant Risk Factors: 1. None reported Non-Significant Risk Factors: 1. Activity level: wheelchair basketball group vs. control group

	Mean aBMD (g/cm2): Femoral neck: 0.79 ± 0.14 Ward's triangle: 0.74 ± 0.14 Trochanter: 0.62 ± 0.12 Total Femur: 0.74 ± 0.12 Mean T-Score: Femoral neck: -2.22 ± 1.65 Ward's triangle: -1.81 ± 1.54 Trochanter: -2.75 ± 1.36 Total Femur: -2.70 ± 1.30 Osteoporosis: __			
Hammond, 2014 Cross-sectional Study USA	All N: 364 Level: 194 cervical, 155 thoracic, 15 lumbar; 170 paraplegic, 194 tetraplegic AIS: 178 AIS A-B, 184 AIS C-D Etiology: 276 traumatic, 88 non-traumatic Age: mean 39.8 ± 16.1 years Duration: mean 6.9 years, IQR 1-8 years % Female: 31.6% BMD: __ Osteoporosis: 67 normative, 170 osteopenia, 127 osteoporosis Normative (T-score ≥ -1.0) N: 67 Level: 37 paraplegic; 30 tetraplegic AIS: 31 AIS A-B, 35 AIS C-D Etiology: 49 traumatic, 18 non-traumatic Age: mean 40.3 ± 16.7 years % Female: 22.4% BMD: __ Osteopenic (T-score between -1.0 and -2.5) N: 170 Level: 76 paraplegic; 94 tetraplegic AIS: 81 AIS A-B, 88 AIS C-D Etiology: 134 traumatic, 36 non-traumatic Age: mean 37.6 ± 15.9 years % Female: 34.7% BMD: __ Osteoporotic (T-score ≤ -2.5) N: 127 Level: 57 paraplegic; 70 tetraplegic AIS: 66 AIS A-B, 61 AIS C-D Etiology: 93 traumatic, 34 non-traumatic Age: mean 42.3 ± 15.8 years % Female: 32.3% BMD: __	Objective: Investigate the prevalence and distribution of osteoporosis in those with SCI. Comparing: demographics of normative vs. osteopenia vs. osteoporosis; Injury duration (≤ 1 year vs. 1-5 years vs. >5 years)	Timeline: June 2005 to June 2009 Data Source: Clinical examinations using DXA in part of routine clinical evaluation (femoral neck and total hip). DXA examinations did not exceed an interval of 6 months after neurologic assessment. Clinical Risk Factors Examined: age, gender, BMI, SCI level, SCI duration, Lower Extremity Motor Score (LEMS), fracture history, ambulatory status, FES usage, pharmacologic agents (anticonvulsants, calcium, vitamin D); potential confounders adjusted for multivariate analysis (FES use, sex, age, BMI, ambulation, injury type, severity, duration, LEMS, fracture history, pharmacologic agents).	Significant Risk Factors: 1. SCI duration: >1 year since injury associated with ≥ 3 fold increase in odds of osteoporosis, compared to <1 year. a. 1-5 years (OR=3.02; 95% CI [1.60, 5.68]; $p=0.001$; adjusted analysis) b. >5 years (OR=3.56; 95% CI [1.78, 7.11]; $p<0.001$; adjusted analysis) 2. Ambulation status: Associated with decreased odds of osteoporosis (OR=0.48; 95% CI [0.27, 0.85]; $p=0.012$, unadjusted analysis, not significant in adjusted analysis). 3. FES: Associated with 42% decreased odds of osteoporosis (OR 0.58; 95% CI [0.35, 0.99]; $p=0.039$; adjusted analysis). 4. Body mass: BMI of between 25 and 40 kg/m ² had 58% decreased odds of osteoporosis (OR=0.42; 95% CI [0.24, 0.73]; $p=0.002$; adjusted analysis). Non-Significant Risk Factors: 1. Sex 2. Age 3. LEMS <10 vs. LEMS ≥ 10 4. SCI level 5. Previous bone fractures 6. Pharmacologic agents a. Calcium b. Vitamin D c. Anticonvulsants
Javidan, 2014	N: 148 Level: 77% complete, 23% incomplete	Objective: Investigate demographic, injury	Timeline: unclear	Significant Risk Factors: 1. Males: Significantly lower aBMD in femur neck and

Cross-sectional Study Iran	AIS: __ Etiology: traumatic Age: Female: mean 42.80 ± 4.81 years Male: mean 51.00 ± 12.89 years Duration: __ % Female: 21.6% Mean Female Z-score: Femur neck: -1.092 ± 1.959 Total hip: -1.30 ± 1.20 Mean Female T-score: Femur neck: -1.335 ± 1.971 Total hip: -1.42 ± 1.25 Mean Male Z-score: Femur neck: -1.527 ± 1.093 Total hip: -1.99 ± 0.983 Mean Male T-score: Femur neck: -1.943 ± 1.069 Total hip: -2.13 ± 0.95 Osteoporosis: __	related factors and biomarkers, in relation to aBMD in participants with SCI. Comparing: Demographics and biomarkers in patients with SCI.	Data Source: Clinical examination using DXA (femur neck, trochanter, intertrochanteric zone, and total hip) and blood analysis. Clinical Risk Factors Examined: gender, SCI level, SCI duration, biomarkers (calcium, phosphor, vitamin D)	total hip (p=0.03 and p=0.001, respectively). 2. BMI: Positive relationship between female BMI and T- and Z-scores in femur neck (r=0.56, p=0.014 and r=0.59, and r=0.87, p=0.0001, respectively). 3. Male age: Negative relationship between age and femoral neck aBMD Z-score in male participants (r=-0.20, p=0.025). 4. SCI level: AIS D participants had lower aBMD in intertrochanteric zone (p=0.005). Non-Significant Risk Factors: 1. SCI duration Biomarkers (calcium, phosphor, vitamin D)
Kannisto, 1998 Cross-sectional Study Finland	N: 35 (34 after 1 excluded from altered blood analysis) Level: 24 complete paraplegic, 3 incomplete paraplegic; 3 complete tetraplegic, 5 incomplete tetraplegic AIS: 27 A, 8 B/C/D Etiology: __ Age: median 31, 18-63 years Duration: median 19 years, 1.5-57 years % Female: 28.6% Mean proximal femur aBMD (g/cm²): All SCI: 0.724 ± 0.230 Complete paraplegic: 0.753 ± 0.272 Incomplete paraplegic: 0.733 ± 0.197 Complete tetraplegic: 0.621 ± 0.129 Incomplete tetraplegic: 0.687 ± 0.128 Mean aBMD at other sites (g/cm²): Femoral neck: 0.69 ± 0.19 Ward's triangle: 0.60 ± 0.24 Intertrochanteric: 0.52, 0.24-0.94 Mean proximal femur Z-score: All SCI: -2.05 Complete paraplegic: -1.56 Incomplete paraplegic: -2.11 Complete tetraplegic: -3.19 Incomplete tetraplegic: -2.74 Mean proximal femur T-score: All SCI: -2.61 Complete paraplegic: -2.42 Incomplete paraplegic: -2.27 Complete tetraplegic: -3.32 Incomplete tetraplegic: -2.96 Osteoporosis: __	Objective: To examine BMD status in adult patients that had sustained SCI in childhood. Comparing: Clinical characteristics within SCI group.	Timeline: unclear Data Source: Clinical examination using DXA (proximal femur), blood and urine analysis. Clinical Risk Factors Examined: age, SCI level, SCI severity, SCI duration, anthropometrics	Significant Risk Factors: 1. Tetraparetic: Lower aBMD than paraplegics, paraparetics, and tetraplegics (F=3.2387, p<0.04); not a significant difference after post-hoc comparison. 2. Lesion level: C1-T6 vs. below T7, significant difference at proximal hip (p<0.004), values and conclusion unclear. 3. Bodyweight: Correlated to proximal femur and femoral neck aBMD (β=0.49, p≥0.01; β=0.57, p<0.01; respectively). Non-Significant Risk Factors: 1. Age at time of injury and time of examination 2. Body height 3. SCI duration

Kaya, 2006 Cross-sectional Study Turkey	SCI group N: 75 Level: 43 complete paraplegic, 10 incomplete paraplegic, 11 complete tetraplegic, 11 incomplete tetraplegic AIS: __ Age: mean 33.01 ± 9.28 years Duration: 33 acute (0-3 months), 10 subacute (4-6 months), 32 chronic (7-24 months) % Female: 28% Mean aBMD (g/cm2): Femoral neck: 0.928 ± 0.2112 Ward's triangle: 0.837 ± 0.2176 Trochanter: 0.773 ± 0.1792 Femoral shaft: 1.067 ± 0.2132 Osteoporosis: __ Control group Defined as able bodied N: 39 Age: Mean 35.69 ± 11.11 years % Female: 33.3% Mean aBMD (g/cm2): Femoral neck: 1.029 ± 0.1414 Ward's triangle: 0.920 ± 0.1734 Trochanter: 0.859 ± 0.1368 Femoral shaft: 1.1822 ± 0.1958 Osteoporosis: __	Objective: Investigate the effects of level, severity, SCI duration and spasticity on aBMD in SCI participants. Comparing: Clinical characteristics between SCI group vs. control group, acute (0-3 months) vs. subacute (4-6 months) vs. chronic (7-24 months).	Timeline: April 2001 to January 2002 Data Source: Clinical examination using DXA (femoral neck, Ward's triangle, trochanter, and femoral shaft), neurological examination, blood and urine analysis. Clinical Risk Factors Examined: SCI level, SCI duration, spasticity, biomarkers	Significant Risk Factors: - SCI duration: - Significant differences in hip aBMD (g/cm2) between the acute and chronic period. - Femoral neck (acute: 1.011 ± 0.1543 vs. chronic: 0.846 ± 0.2378; p=0.005); weak correlation between Femoral neck and SCI duration (r=-0.40, p=0.000) - Ward's Triangle (acute: 0.905 ± 0.1668 vs. chronic: 0.766 ± 0.2461; p=0.033) - Trochanter (acute: 0.858 ± 0.1156 vs. chronic: 0.698 ± 0.1957; p=0.000) - Femoral shaft (acute: 1.135 ± 0.1716 vs. chronic: 0.984 ± 0.2367; p=0.016) - Higher calcium level (24-hour urine) from acute patients to subacute (p=0.01) and chronic patients (p=0.000). - Phosphorus levels differ between acute and subacute, acute and chronic participants (both p=0.001). Non-Significant Risk Factors: - Paraplegic vs. tetraplegic - Complete vs incomplete - Spasticity: flaccid vs. spastic - Blood analysis - PTH - Calcitonin - Triiodothyronine - Thyroxine - Thyroid stimulating hormone - Calcium levels
Kostovski, 2015 Cohort Study Norway	Complete SCI group N: 13 Level: AIS A, B Age: mean 34 years, range 18-60 years Duration: mean 36, 14-57 days % Female: 0% Mean Proximal femur aBMD (g/cm2): 3 month: 0.98 ± 0.06 Osteoporosis: __ Incomplete SCI group N: 18 Level: AIS C, D, E Age: mean 41 years, range 19-63 years Duration: mean 29, 10-52 days % Female: 0% Mean Proximal Femur aBMD (g/cm2): 3 month: 1.05 ± 0.06 Osteoporosis: __	Objective: To compare aBMD and biomarker changes in recent complete and incomplete SCI patients. Comparing: motor-complete SCI vs. Motor-incomplete	Timeline: January 2007 to July 2009; 3 and 12 month post SCI Data Source: Clinical examination using DXA (proximal femur), blood analysis, physical activity (Leisure Time Physical Activity scale, Stages of Exercise Change Questionnaire [SEQ]) and spasticity questionnaires/scales (Penn Spasm Frequency Scale, Ashworth Scale). Clinical Risk Factors Examined: SCI level, SCI severity, SCI duration,	Significant Risk Factors: - SCI duration: aBMD decrease at 12 months at proximal femur in both complete and incomplete groups (0.78 ± 0.06 and 0.95 ± 0.06 g/cm2, respectively, p<0.05) - SCI level: - Incomplete: - Lower Ca2 at 3 months after injury (p=0.02) - Lower mean phosphate at each examination (p=0.037) - Lower mean CTx (p=0.011) - Higher serum MMP-2 in complete one month after injury (p=0.034) - Lower AIS motor-score associated with lower proximal femur aBMD (p=0.002), from mixed model statistical analyses. - Spasticity: Increased frequency and severity of spasticity correlated with lower aBMD at 12 months (r=0.74, p=0.02) - Physical activity: Proximal femur aBMD at 12 months

	Compared to able bodied controls		physical activity levels, spasticity, biomarkers	positively correlated with SECQ scores ($r=0.61$, $p=0.05$). Non-Significant Risk Factors: 1. BMI 2. Age
Lala, 2014 Cross-sectional Study Canada	All N: 70 Level: C1-L2; 23 motor complete paraplegic, 11 motor incomplete paraplegic, 22 motor complete tetraplegic, 14 motor incomplete tetraplegic AIS: 23 A-B, 11 C-D, 22 A-B, 14 C-D Etiology: __ Osteoporosis: __ Fracture Group N: 19 Level: 17 complete Age: mean 48.9 ± 10.6 years Duration: mean 19.4 ± 11.8 years % Female: 32% Mean aBMD (g/cm²) Distal Femur: 0.454 ± 0.11 Proximal Tibia: 0.371 ± 0.10 Total Hip: 0.730 ± 0.19 Femoral Neck: 0.689 ± 0.13 Non-Fracture Group N: 51 Level: 28 complete Age: mean 48.8 ± 11.9 years Duration: mean 14.0 ± 8.9 years % Female: 27% Mean aBMD (g/cm²) Distal Femur: 0.667 ± 0.20 Proximal Tibia: 0.541 ± 0.16 Total Hip: 0.769 ± 0.17 Femoral Neck: 0.595 ± 0.14	Objective: Examine if DXA-based aBMD or pQCT-based bone geometry is associated with chronic SCI lower extremity fragility fractures. Comparing: fracture group vs. non-fracture group demographics	Timeline: April 2009 to June 2012 Data Source: Clinical examination using pQCT and DXA (distal femur, proximal tibia, total hip, femoral neck). Clinical Risk Factors Examined: fracture status, SCI severity, age, gender, SCI duration, prior bisphosphonates therapy	Significant Risk Factors: - SCI severity: - Complete injuries associated with fragility fractures ($p=0.01$). - After adjusting for complete injury 1 SD decrease in distal femur aBMD was associated with increased odds of fracture OR 4.9, 95%CI (1.7–17.5) - Fracture history: Participants with fragility fractures had lower aBMD in distal femur ($p<0.001$), proximal tibia ($p<0.001$), total hip ($p=0.021$) and femoral neck ($p=0.01$). Non-Significant Risk Factors: - Age - Gender - SCI duration Prior bisphosphonate therapy
Lazo, 2001 Cross-sectional Study USA	All N: 41 Level: C2-L1 Etiology: __ Age: mean 56 ± 13.3 years Duration: mean 17.8 ± 14.1 years % Female: 0% Osteoporosis: 25 osteoporotic, 8 osteopenic Fracture group N: 14 Level: 42.9% cervical, 35.7% thoracic, 21.4% lumbar AIS: 78.6% A, 14.3% B, 7.1% D	Objective: Determine fracture risk in SCI population by evaluating the relationship between aBMD, demographics and fracture history. Comparing: demographic and clinical characteristics; fracture group vs non-fracture group;	Timeline: July 1999 to March 2000 Data Source: Clinical examination using DXA (femoral neck). Clinical Risk Factors Examined: SCI duration, SCI level, SCI severity, age, fracture history	Significant Risk Factors: SCI duration: - Participants with osteoporosis had a longer SCI duration than those with a normal aBMD ($t=2.47$, $p<0.05$). - Fracture group had a longer SCI duration ($t=2.39$, $p<0.05$). - Fracture history: - Significant aBMD difference between fracture and non-fracture participants ($t=4.09$, $p<0.001$). - Occurrence of fracture based on aBMD: OR 2.2, 95%CI [1.25, 3.89], $p=0.006$ - Occurrence of fracture based on T-score: OR 2.8, 95%CI [1.32, 5.89], $p=0.007$

	AIS: 78.6% A, 14.3% B, 7.1% D Age: mean 61 ± 14.7 years Duration: mean 24.8 ± 14.2 years Mean Femoral neck aBMD (g/cm²): 0.50 ± 0.23 Mean Femoral neck T-score: -4.4 ± 1.7 Non-Fracture group N: 27 Level: 59.3% cervical, 22.2% thoracic, 18.5% lumbar AIS: 40.7% A, 25.9% B, 11.1% C, 22.2% D Age: mean 53 ± 12.0 years Duration: mean 14.3 ± 12.9 years Mean Femoral neck aBMD (g/cm²): 0.79 ± 0.20 Mean Femoral neck T-score: -2.2 ± 1.6	osteoporosis vs. osteopenia vs. normal aBMD		3. Age: a. Participants with normal aBMD were younger than those with osteopenia and osteoporosis (f=3.90, p<0.05); normal aBMD participant's mean age = 45 years; osteopenia participant's mean age = 59.75 years; osteoporosis participant's mean age = 58.24 years Non-Significant Risk Factors: 1. Age: Not significant occurrence of fracture based on age: OR 1.05, 95%CI [0.98, 1.13], p>0.05) 2. AIS SCI level
Liu, 2000 Cross-sectional Study USA	N: 29 examined using DXA (64 total in study) Level: __ AIS: __ Etiology: traumatic Age: mean 52, 23-98 years % Female: 0% Mean Femoral neck Z-score: 0.9 ± 1.6 below the mean of controls Osteoporosis: __ Compared to age-matched controls from previous study	Objective: Investigate the usefulness of QCT to study SCI aBMD compared to DXA methods. Comparing: clinical characteristics; DXA vs QCT; SCI vs controls	Timeline: unclear Data Source: Clinical examination using DXA (femoral neck) and QCT. Clinical Risk Factors Examined: SCI duration, SCI level	Significant Risk Factors: 1. SCI duration: aBMD loss with increased SCI duration. Non-Significant Risk Factors: 1. SCI level: paraplegic vs. tetraplegic SCI severity: complete vs. incomplete
Miyahara, 2008 Cross-Sectional study Japan	SCI group (wheelchair athletes) N: 28 Level: 13 high paraplegic, 15 low paraplegic AIS: __ Etiology: __ Age: mean 34.7 ± 9.3 years Duration: mean 14.6 ± 8.4 years % Female: 0% Mean aBMD (g/cm²): Leg: 1.052 ± 0.179 Entire body: 1.153 ± 0.132 Osteoporosis: __ Controls Controls defined as physically able healthy athletes N: 25 Age: mean 33.0 ± 9.0 years % Female: 0% Mean aBMD (g/cm²): Leg: 1.373 ± 0.091 Entire body: 1.214 ± 0.079 Osteoporosis: __	Objective: Investigate whether SCI duration and physical activity affect BMD. Comparing: wheelchair athletes vs. control athletes; demographics, SCI duration, SCI level, activity levels within SCI group	Timeline: unclear Data Source: clinical examination using DXA (entire body, legs [sites not defined for both]), questionnaire for nutrition and physical activity. Clinical Risk Factors Examined: age, SCI duration, SCI level, % body fat, lean body mass, physical activity levels and types, duration before restarting physical activity, period after restarting physical exercise Multiple regressions adjusted for age, SCI level, sports type, mass, % body fat, activity time per week	Significant Risk Factors: 1. SCI duration: a. With increase in SCI duration, aBMD decreased in legs and whole body (r=-0.549, p<0.01; r=-0.452, p<0.05; respectively) b. Multiple regression analysis indicated negative relationship with SCI duration and leg and whole body aBMD change (partial correlation coefficient (pcc) =-0.582, p<0.01; pcc=-0.489, p<0.05; respectively) 2. Duration before restarting physical activity: Negatively correlated with aBMD of legs and entire body (pcc=-0.467, p=0.019; pcc=-0.488, p=0.011) 3. Period after restarting physical activity: multiple regression, correlated with leg aBMD (pcc=-0.457, p=0.022) 4. Lean body mass of whole body: Positive correlation with leg and whole body aBMD (r=0.466, p<0.05; r=0.470, p<0.05; respectively) Non-Significant Risk Factors: 1. Age 2. SCI level: high vs. low paraplegic 3. Type of physical activity 4. % Body fat

Morse, 2012 Cross-sectional Study USA	All SCI N: 39 Level: 29 complete, 10 incomplete AIS: __ Etiology: __ Wheelchair group N: 30 Level: 28 complete, 2 incomplete Age: mean 50.6 ± 10.9 years Duration: mean 22.8 ± 10.2 years % Female: 0% Mean aBMD (g/cm2): Distal femur: 0.57_0.18 Proximal tibia: 0.54_0.22 Osteoporosis: __ Walking group N: 9 Level: 1 complete, 8 incomplete Age: mean 66.4 ± 10.1 years Duration: mean 21.3 ± 14.6 years % Female: 0% Mean aBMD (g/cm2): Distal femur: 0.87 ± 0.17 Proximal tibia: 0.93 ± 0.17 Osteoporosis: __ Control group Defined as not needing ambulatory aid, no neurological disorders, no history of osteoporosis N: 10 Age: mean 55.8 ± 12.1 years % Female: 0% Mean aBMD (g/cm2): Distal femur: 0.97 ± 0.19 Proximal tibia: 1.08 ± 0.20 Osteoporosis: 100% normal	Objective: Determine the relationship between sclerostin and BMD in chronic SCI participants with differing ambulatory statuses. Comparing: Clinical characteristics within SCI group; wheelchair group vs. walking group; SCI vs. controls.	Timeline: unclear Data Source: Clinical examination using DXA (distal femur, proximal tibia), blood analysis and physical exam. Clinical Risk Factors Examined: ambulatory status and wheelchair use, sclerostin, association between sclerostin and risk factors, age	Significant Risk Factors: 1. Wheelchair use: Lower aBMD at distal femur and proximal tibia than walking group ($p=0.0001$, $p<0.0001$, respectively) 2. Sclerostin: Positively associated with distal femur and proximal tibia aBMD ($R^2=0.11$, $p=0.04$; $R^2=0.22$, $p=0.003$; respectively). Non-Significant Risk Factors: 1. Age Association between sclerostin and risk factors (SCI severity, SCI duration, wheelchair use, age, BMI, smoking status, other biomarkers [CTx and OC])
Morse, 2013 Cross-sectional study USA	N: 39 Level: 29 complete, 10 incomplete AIS: 29A/B, 10C/D Etiology: __ Age: mean 54.3 ± 12.6 years Duration: mean 22.4 ± 11.2 years % Female: 0% Mean aBMD (g/cm2): Distal femur: 0.641 ± 0.218	Objective: To compare sclerostin and other bone related biomarkers to aBMD and BMC in participants with SCI. Comparing: Bone biomarkers within	Timeline: unclear Data Source: Clinical examination using DXA (distal femur [20%], proximal tibia, femoral neck, total hip), blood analysis. Clinical Risk Factors	Significant Risk Factors: 1. Sclerostin (age adjusted analysis): a. Positively associated with leg BMC ($R^2=0.33$, $p=0.0002$) b. Positively associated with distal femur aBMD ($n=47$; $R^2=0.23$, $p=0.006$) c. Positively associated with proximal tibia aBMD ($n=47$; $R^2=0.28$, $p=0.001$) d. Positively associated with total hip aBMD ($n=46$; $R^2=0.30$, $p=0.009$)

	Proximal tibia: 0.631 ± 0.263 Total hip: 0.729 ± 0.209 Femoral neck: 0.732 ± 0.189 Mean leg BMC (g): 830.6 ± 266.6 Osteoporosis: 7 osteopenia, 22 osteoporosis Control Non-SCI participants with no neurological conditions that can affect walking, and no history of osteoporosis N: 10 Age: 61.7 ± 8.2 % Female: 0% Mean aBMD (g/cm²): Distal femur: 0.970 ± 0.190 Proximal tibia: 1.084 ± 0.203 Total hip: 1.045 ± 0.154 Femoral neck: 0.971 ± 0.166 Mean leg BMC (g): 1163.9 ± 230.0 Osteoporosis: 1 osteoporotic, 4 osteopenic	Comparing: Bone biomarkers within SCI group and vs. controls.	biomarkers (sclerostin, CTx, OC, osteoprotegerin, Dickkopf-related protein 1, vitamin D, receptor activator of nuclear factor kappa B ligand [RANKL])	e. Positively associated with femoral neck aBMD (n=46; R²=0.26, p=0.007) 2. Osteoprotegerin a. Significant association with leg BMC in unadjusted analysis (data not shown); when age-adjusted, no association. Non-Significant Risk Factors: 1. Biomarkers a. CTx b. OC c. Osteoprotegerin d. Dickkopf-related protein 1 e. Vitamin D f. RANKL
Morse, 2016 Longitudinal Study USA	SCI N: 152 Level: 74 complete, 78 incomplete AIS: 74 A/B, 13 C, 65 D Etiology: ___ Age: mean 55.1 ± 14.4 years Duration: mean 17.9 ± 13.3 years % Female: 12.5% Mean aBMD (g/cm²): Distal femur: 0.783 ± 0.218 Proximal tibia: 0.844 ± 0.291 Femoral neck: 0.863 ± 0.196 Total hip: 0.884 ± 0.235 Osteoporosis: 58 osteoporotic, 82 osteopenia/normal, 12 missing	Objective: Test the association between statin use, traditional risk factors and bone loss in SCI participants. Comparing: Clinical characteristics at baseline and follow up within SCI group.	Timeline: August 2009 to April 2012; baseline and follow up (mean 21, 16-44 months) Data Source: Clinical examination using DXA (distal femur, proximal tibia, femoral neck, total hip), blood analysis, physical exam. Clinical Risk Factors Examined: statin use, total body mass, wheelchair use, age, gender, SCI duration, SCI level, anthropometrics, biomarkers	Significant Risk Factors: 1. Statin use: a. Associated with aBMD at knee, p=0.07. b. Gained BMD at a rate of 1.64% (95%CI [0.30-2.99%], p=0.01) per year, compared to non-users. 2. Total body mass: a. Associated with aBMD at knee, p=0.001. b. Gained BMD at a rate of 0.15% (95%CI [0.05-0.26%], p=0.005) per year, compared to non-users. 3. Wheelchair use: a. Associated with aBMD loss, p=0.04. b. Loss of BMD at a rate of 1.45% (95%CI [-2.86--0.04%], p=0.04) compared to participants who walk. Non-Significant Risk Factors: 1. Age 2. Gender 3. SCI duration 4. Baseline BMI 5. Total body weight 6. % total body fat 7. Vitamin D levels 8. SCI motor completeness 9. Walking status
Paker, 2006 Cross-sectional Study Turkey	All SCI N: 48 Level: 39 paraplegic, 8 tetraplegic AIS: 26 A/B, 22 C/D Etiology: traumatic Age: mean 38.47 ± 15.88 years Duration: mean 24.52 ± 20.9 months % Female: 45% Osteoporosis: ___	Objective: Investigate aBMD, bone biomarkers, and Functional Independence Measurement (FIM) in acute and chronic SCI.	Timeline: January 2005 to December 2005 Data Source: Clinical examination using DXA (femoral neck, total femur), FIM, blood analysis.	Significant Risk Factors: 1. SCI duration: a. Negative correlation with aBMD at femoral neck and total femur (p<0.01, p<0.02, respectively) b. Negative correlation with T-scores at femoral neck and total femur (p<0.028, p<0.03, respectively). c. CTx of type 1 collagen significantly higher in acute SCI group (1.50 ± 0.65 vs. 1.12 ± 0.39, p=0.017).

Turkey	Acute SCI (<1 year) N:31 Duration: mean 4.35 ± 1.67 months aBMD (g/cm²): Femoral neck: mean 0.954 ± 0.195 Total femur: mean 0.992 ± 0.182 Mean T-score: Femoral neck: mean -0.766 ± 1.46 Total femur: mean -0.5 ± 1.45 Chronic SCI (>1 year) N:17 Duration: mean 61.29 ± 88.04 months Mean aBMD (g/cm²): Femoral neck: 0.785 ± 0.146 Total femur: 0.762 ± 0.136 Mean T-score: Femoral neck: -2.088 ± 1.03 Total femur: -2.258 ± 1.09 Controls (healthy, age-matched) N: 47 Age: 38.47 ± 15.88 years % Female: 47% Mean aBMD (g/cm²): Femoral neck: 0.999 ± 0.116 Total femur: 1.063 ± 0.132 Mean T-score: Femoral neck: -0.408 ± 0.8 Total femur: -0.094 ± 1.02	Comparing: Demographics and clinical characteristics in SCI groups; acute SCI vs. chronic SCI vs. control.	Clinical Risk Factors Examined: SCI duration, FIM, age, spasticity, anthropometrics, bone biomarkers (OC, CTx of type 1 collagen, ALP, calcium, phosphorus)	d. Phosphorus significantly higher in acute group (4.57 ± 0.82 vs. 3.52 ± 0.62, $p=0.000$) 2. FIM: Negative correlation with aBMD at femoral neck and total femur ($p<0.005$ and $p<0.000$, respectively) and T-scores ($p<0.02$ and $p<0.000$). Non-Significant Risk Factors: - Age - Spasticity - Anthropometrics - AIS - Biomarkers - OC - ALP Serum calcium
Pelletier, 2014 Cross-sectional Study Canada	All SCI N: 1137 Level: C1-T12; 572 paraplegia, 565 tetraplegia; 444 complete, 693 incomplete AIS: 444A/B, 693 C/D Etiology: traumatic Age: mean 48.3 ± 13.3 years Duration: mean 18.5 ± 13.1 years % Female: 29% BMD: __ Osteoporotic Status (%/year): 21.5 Fracture History (%/year): 7.4 Fracture group N: 84 Level: 38 paraplegia (28 complete, 10 incomplete), 46 tetraplegia (21 complete, 25 incomplete) AIS: 49 A/B, 35 C/D Etiology: traumatic Age: mean 47.8 ± 11.4 years Duration: mean 19.6 ± 12.6 years % Female: 32%	Objective: Describe the incidence of fracture and prevalence of osteoporosis in SCI participants. Comparing: Demographic risk factors within SCI group.	Timeline: unclear Data Source: SCI health Questionnaire (community follow up and comorbidities questionnaire). Clinical Risk Factors Examined: osteoporosis status, motor and sensory complete injuries, SCI duration, gender, multiple risk factors	Significant Risk Factors: - Motor complete injury (AIS A or B): - Fracture OR 1.7, 95%CI (1.10-2.72), $p=0.17$ - Osteoporosis OR 1.9, 95%CI (1.42-2.55), $p<0.001$ - Sensory complete injury (AIS A): - Fracture OR 2.2, 95%CI (1.38-3.50), $p=0.001$ - Osteoporosis OR 2.0, 95%CI (1.47-2.63), $p<0.001$ - SCI duration (>10 years): Osteoporosis OR 3.0, 95%CI (2.10-4.23), $p<0.001$ - Female: Osteoporosis OR 2.4, 95%CI (1.74-3.17), $p<0.001$ 3 or more risk factors (age at injury, SCI duration, motor complete, sensory complete, paraplegia, female): - Osteoporosis OR 2.4, 95%CI (1.78-3.18), $p<0.001$ Non-Significant Risk Factors: Paraplegia

	BMD: ____ Osteoporosis group N: 244 Level: 113 paraplegia (71 complete, 42 incomplete), 131 tetraplegia (52 complete, 79 incomplete) AIS: 123 A/B, 121 C/D Etiology: traumatic Age: mean 49.6 ± 11.7 years Duration: mean 23.4 ± 13.1 years % Female: 43% BMD: ____			
Reiter, 2007 Cross-sectional Study Germany	All SCI N: 62 Level: 32 paraplegic, 30 tetraplegic AIS: 39 A, 23 B/C/D Etiology: traumatic Age: mean 36.2 ± 14.0 years Osteoporosis: ____ Short-term SCI N: 28 (15 with biomarker analysis) Age: mean 36.3 ± 17.6 years Duration: ≤1 year % Female: 0% Mean aBMD (g/cm²): Femoral neck: 0.842 ± 0.151 Total proximal femur: 0.889 ± 0.169 Trochanteric region: 0.657 ± 0.145 Intertrochanteric region: 1.007 ± 0.197 Ward's triangle: 0.711 ± 0.194 Mean Z-score: Femoral neck: -0.238 ± 1.186 Total proximal femur: -0.658 ± 1.316 Trochanteric region: -0.883 ± 0.984 Intertrochanteric region: -1.179 ± 1.151 Ward's triangle: 0.234 ± 1.334 Long-term SCI N: 34 (9 with biomarker analysis) Age: mean 35.9 ± 9.8 years Duration: >5 years % Female: 0% Mean aBMD (g/cm²): Femoral neck: 0.620 ± 0.167 Trochanteric region: 0.528 ± 0.197 Intertrochanteric region: 0.742 ± 0.307 Ward's triangle: 0.511 ± 0.223 Total proximal femur: 0.633 ± 0.188 Mean Z-score: Femoral neck: -2.688 ± 1.882 Trochanteric region: -2.135 ± 1.846	Objective: Investigate the changes in BMD in relation to biomarkers and SCI duration. Comparing: Clinical characteristics within SCI participant groups; short-term SCI vs. long-term SCI.	Timeline: January – December 1997 Data Source: Clinical examination using DXA (femoral neck, trochanteric region, intertrochanteric region, Ward's triangle, total proximal femur). Clinical Risk Factors Examined: SCI duration and SCI level	Significant Risk Factors: 1. SCI duration: a. Long-term SCI participants had lower aBMD at each site. i. Femoral neck, p<0.0001 ii. Total proximal femur, p<0.0001 iii. Trochanteric region, p=0.0028 iv. Intertrochanteric region, p<0.0001 v. Ward's triangle, p=0.0002 b. Long term SCI participants had a lower Z-score at total proximal femur (p<0.0001). Non-Significant Risk Factors: 1. SCI level: paraplegic vs. tetraplegic

	Intertrochanteric region: -3.337 ± 1.604 Ward's triangle: -2.036 ± 2.403 Total proximal femur: -2.773 ± 1.786			
Sabo, 2001 Cross-sectional Study Germany	N: 46 Level: C4-T12; paraplegic, tetraplegic AIS: Frankel: 33 A, 13 B-D Etiology: ___ Age: mean 32 ± 10.7 years Duration: mean 8, 1-26 years % Female: 0% Mean Proximal femur Z-score: -2.08 ± 0.48 Osteoporosis: 46 osteoporotic	Objective: Investigate potential correlation between clinical parameters and Z-scores in participants with SCI. Comparing: Clinical characteristics within SCI group.	Timeline: unclear Data Source: Clinical examination using DXA (proximal femur) and interview. Clinical Risk Factors Examined: ambulatory status, immobilization status (>2 weeks bedrest post-surgery ≥ 3 months before DXA examination), SCI level (Frankel Score, severity of injury), SCI duration	Significant Risk Factors: 1. Immobilization status: Participants immobilized post-surgery (n=14) had significantly lower proximal femur Z-score (1.71 ± 0.50 vs. -2.95 ± 0.99 , $p<0.01$). 2. SCI duration: Negative correlation with aBMD at proximal femur ($r=-0.36$, $p<0.05$). Non-Significant Risk Factors: 1. SCI level: a. complete vs incomplete b. tetraplegia vs. paraplegia Non-ambulatory vs ambulatory: (Mean proximal femur Z-score: -2.27 ± 0.46 vs. -1.77 ± 0.71 , respectively)
Schnitzer, 2012 Cross-sectional Study USA	All N: 66 Level: 25 cervical, 35 thoracic, 5 lumbar, 1 unknown; 18 complete, 44 incomplete, 4 unknown AIS: ___ Etiology: ___ Age: mean 40.0 ± 15.1 years Duration: mean 7.2 ± 8.7 years; 20 acute, 46 chronic % Female: 30.0% Osteoporosis: 81% osteoporotic Acute SCI (<1 year) N: 20 Mean aBMD (g/cm ²): Total hip: right 0.975 ± 0.196 , left 0.996 ± 0.176 Femoral neck: right 0.869 ± 0.184 , left 0.887 ± 0.167 Mean T-score: Total hip: right -0.3 ± 1.3 , left -0.4 ± 1.3 Femoral neck: right -0.4 ± 1.4 , left -0.3 ± 1.3 Chronic SCI (≥ 1 year) N: 46 Mean aBMD (g/cm ²): Total hip: right 0.754 ± 0.200 , left 0.746 ± 0.186 Femoral neck: right 0.732 ± 0.165 , left 0.719 ± 0.182 Mean T-score: Total hip: right -2.0 ± 1.3 , left -2.1 ± 1.2 Femoral neck: right -1.7 ± 1.1 , left -1.8 ± 1.3 Osteoporosis: 68% osteoporotic	Objective: Investigate aBMD relationship between acute and chronic SCI participants; Evaluate QUS as a method for identifying osteoporosis, compared to DXA. Comparing: chronic SCI vs. acute SCI	Timeline: unclear Data Source: Clinical examination using DXA, demographics and clinical parameters from database (SCI level, SCI severity, SCI duration). Clinical Risk Factors Examined: Demographics, SCI duration, SCI level, SCI severity	Significant Risk Factors: 1. SCI duration: Chronic SCI group had lower aBMD and T-scores at total hip and femoral neck, both $p<0.005$. Non-Significant Risk Factors: 1. SCI level 2. Gender Age

Shojaei, 2006 Cross-sectional Study Iran	SCI N: 132 Level: 12.9% cervical, 78% thoracic, 9.1% lumbar; 87.1% paraplegic, 12.9% tetraplegia AIS: ____ Etiology: ____ Age: mean 37.4, 25-51 years Duration: range 5-23 years % Female: 0% Mean femoral neck aBMD (g/cm ²): 0.66, 0.3-1.2 Osteoporosis: Inconsistency with some values reported in BMD results table and in text. Table BMD Hip: 16.7% osteoporotic, 18.2% osteopenic, 65.1% normal Text BMD Hip: 81.5%, osteoporosis, 13.1% osteopenia, 5.4% normal	Objective: Investigate relationship between clinical characteristics, demographics, anthropometrics, and osteoporosis in SCI participants. Comparing: Clinical characteristics, demographics, and anthropometrics within SCI group.	Timeline: unclear Data Source: Clinical examination using DXA (femoral neck), demographic questionnaire. Clinical Risk Factors Examined: Age, SCI duration, SCI level, spasticity, anthropometrics,	Significant Risk Factors: 1. None Non-Significant Risk Factors: 1. Age 2. SCI duration 3. SCI level 4. Spasticity 5. Anthropometrics
Singh, 2014a Prospective Longitudinal Study India	N: 95 Level: 20 cervical, 27 dorsal, 35 dorso-lumbar junction, 13 lumbar; 75 paraplegic, 20 tetraplegic; AIS: 53 A, 42 B Etiology: ____ Age: mean 33.3, 19-60 years Duration: acute SCI % Female: 25.3% Mean aBMD (g/cm ²): Hip: 0.968 Proximal tibia: 1.02 Tibial diaphysis: 1.11 Distal tibial epiphysis: 0.985 Osteoporosis: ____	Objective: Investigate the changes in BMD within the first year of SCI. Comparing: Clinical characteristics within acute SCI group.	Timeline: 2007-2009; baseline, 3, 6, 12 post-SCI follow up Data Source: Clinical examination using DXA (hip, proximal tibia, tibial diaphysis, distal tibial epiphysis), blood and urine analysis. Clinical Risk Factors Examined: SCI duration, SCI level and severity, biomarkers (ALP, calcium, phosphorus)	Significant Risk Factors: 1. SCI duration: Decline in aBMD from baseline to 12 month post-SCI. a. Hip: 0.77 g/cm ² , p<0.05 b. Proximal tibia: 0.74 g/cm ² , p<0.001 c. Distal tibial epiphysis: 0.75 g/cm ² , p<0.001 2. Complete SCI (AIS A/B): Greater decline in aBMD than incomplete SCI at 12 month post-SCI. a. Hip: p<0.05 b. Proximal tibial epiphysis: p<0.05 Non-Significant Risk Factors: 1. SCI level: paraplegic vs. tetraplegic 2. ALP 3. Calcium 4. Phosphorus
Singh, 2014b Prospective longitudinal Study India	N: 95 Level: 20 cervical, 27 thoracic, 35 thoracic-lumbar junction, 13 lumbar; 75 paraplegia, 20 tetraplegia AIS: 53 A, 42 B Etiology: ____ Age: mean 33.3, range 19-60 years Duration: <72 hours % Female: 25.3% Mean BMC (g): Left Leg: 416 Right Leg: 401.4 Osteoporosis: ____	Objective: Investigate the body composition changes post SCI. Comparing: Clinical characteristics in relation to BMC within SCI group.	Timeline: baseline (<72 hours post injury) and follow up at 3, 6, and 12 months Data Source: clinical examination using DXA (BMC), physical examination Clinical Risk Factors Examined: SCI level	Significant Risk Factors: 1. SCI level and leg lean tissue mass: Leg BMC in participants with incomplete injuries correlated with leg lean tissue mass (r=0.565, p<0.001) Non-Significant Risk Factors: None reported
Spungen, 2003 Cross-sectional Study USA	N: 133 Level: 67 paraplegic, 66 tetraplegic; 94 complete, 39 incomplete AIS: ____ Etiology: ____ Mean Age: Paraplegic: 37 ± 1.30 years Tetraplegic: 40 ± 1.44 years	Objective: Investigate the correlations between BMC and lean tissue mass, SCI level and severity. Comparing: Clinical	Timeline: unclear Data Source: Clinical examination using DXA (whole body and leg BMC). Clinical Risk Factors	Significant Risk Factors: 1. Leg lean tissue mass: a. Positively correlated to leg BMC in both tetraplegics and paraplegics (r=0.55, p<0.0001; r=0.53, p<0.0001; respectively). b. Positively correlated to leg BMC in incomplete participants (r=0.74, p<0.0001)

	Complete: 38 ± 0.90 years Incomplete: 39 ± 1.31 years Mean Duration: Paraplegic: 12 ± 0.94 years Tetraplegic: 14 ± 1.16 years Complete: 13 ± 0.90 years Incomplete: 11 ± 1.31 years % Female: 0% Mean BMC (g): Paraplegic: Leg: 606 ± 29 Whole body: 1,615 ± 46 Tetraplegic: Leg: 558 ± 32 Whole body: 1,437 ± 58 Complete: Leg: ___ Whole body: 1,431 ± 39 Incomplete: Leg: ___ Whole body: 1,756 ± 76 Osteoporosis: ___ Control group Able-bodied, matched for age, height, and ethnicity N: 100 Age: 441.19 % Female: 0% Mean BMC (g): Leg: 1,203 ± 19 Whole body: 3,030 ± 44 Osteoporosis: ___	characteristics within SCI group; paraplegic vs. tetraplegic; complete vs. incomplete.	Examined: lean tissue mass, SCI level and severity	2. Complete SCI: Had significantly lower leg and total body BMC than incomplete participants, both $p < 0.0001$. Non-Significant Risk Factors: 1. Complete participant leg lean tissue mass 2. SCI level: paraplegic vs. tetraplegic
Szollar, 1997 Case-control Study USA	20-39 year SCI N: 65 Level: 33 paraplegia, 32 tetraplegia AIS: ___ Etiology: ___ Age: mean 30.4 ± 0.8 years Duration: mean 5.2 ± 0.8 years % Female: 0% BMD: ___ Osteoporosis: ___ 40-59 year SCI N: 108 Level: 49 paraplegia, 59 tetraplegia AIS: ___ Etiology: ___ Age: mean 47.7 ± 0.5, range 40-58 years Duration: mean 16.5 ± 1.0, range 0.08-34 years % Female: 0%	Objective: Investigate the relationship between aBMD and age, SCI duration, SCI level. Comparing: 20-39 year SCI vs. 40-59 year SCI vs. 60± year SCI vs. control; SCI stratified by duration (<1, 1-5, 6-9, 10-19, 20-29, 30-39, 40-49, 50-59 years) and SCI level (paraplegia, tetraplegia)	Timeline: 1994 to 1996 Data Source: Clinical examination using DXA (femoral neck, Ward's triangle, trochanter) and blood analysis. Clinical Risk Factors Examined: SCI level, SCI duration, age	Significant Risk Factors: 1. SCI duration: a. Decreased aBMD at proximal femur in patients with SCI duration >1 year compared to <1 year ($p < 0.04$) b. Over time decrease in femoral neck aBMD with lowest aBMD at 19 years post injury, regardless of age or SCI level Non-Significant Risk Factors: 1. Paraplegic vs tetraplegic: Age

	BMD: ____ Osteoporosis: ____ 60± year SCI N: 89 Level: 54 paraplegia, 36 tetraplegia AIS: ____ Etiology: ____ Age: mean 67.1 ± 0.6, range 60-78 years Duration: mean 21.3 ± 1.9, range 0.08-53 years % Female: 0% BMD: ____ Osteoporosis: ____ Controls Defined as able-bodied, age-matched controls N:92 Age: mean 51.1, range 24-76 years % Female: 0% BMD: ____ Osteoporosis: ____			
Szollar, 1998 Cross-sectional Study USA	SCI N: 176 Level: 83 paraplegic, 93 tetraplegic; 176 complete AIS: 176 A Etiology: Age: mean 41.2, 20-59 years Duration: 0-1 years (n=37) 1-9 years (n=45) 10-19 (n=41) 20-29 (n=44) 30-39 (n=9) % Female: 0% BMD: ____ Osteoporosis: ____ Non-SCI Control N: 62 Age: range 24-59 years % Female: 61% BMD: ____ Osteoporosis: ____	Objective: Evaluate patterns of osteoporosis after SCI. Comparing: parathyroid hormone levels; biochemical markers of bone formation; pattern of bone mineral loss within SCI group vs. control	Timeline: unclear Data Source: Clinical examination using DXA (femoral neck, Ward's triangle, greater trochanter), immunoassay methods. Clinical Risk Factors Examined: age, SCI duration, serum concentrations (calcitonin and parathyroid hormone), bone formation biomarkers	Significant Risk Factors: 1. SCI duration: a. All groups showed progressive decline in aBMD at proximal femur. b. 20-29 and 30-39 patients reached bone mass fracture threshold 1-9 years post SCI. Non-Significant Risk Factors: 1. Parathyroid hormone Serum calcitonin levels
Tsuzuku, 1999 Cross-sectional Study Japan	All N: 20 Level: C5-L2; 10 paraplegic, 10 tetraplegic AIS: ____ Etiology: ____ Age: mean 37.15 ± 13.63 years Duration: mean 11.98 ± 8.48 years % Female: 0% Paraplegia	Objective: Investigate the differences in aBMD between paraplegia and tetraplegia participants Comparing: paraplegia vs. tetraplegia	Timeline: unclear Data Source: Clinical examination using DXA (femoral neck, trochanter, Ward's triangle) Clinical Risk Factors Examined: SCI level	Significant Risk Factors: 1. Tetraplegic: Trochanter aBMD lower in tetraplegics than paraplegics (p<0.05). Non-Significant Risk Factors: Paraplegic vs. tetraplegic: No significant aBMD differences at femoral neck and Ward's triangle.

	N: 10 Level: paraplegia Age: mean 44.1 ± 14.3 years Duration: mean 16.1 ± 10.1 years BMD: __ Osteoporosis: __ Quadriplegia N: 10 Level: quadriplegia Age: mean 30.2 ± 9.0 years Duration: mean 7.9 ± 3.5 years BMD: __ Osteoporosis: __			
Vestergaard, 1998 Cross-sectional Survey Denmark	SCI group N: 438 Level: cervical 198 (46%), thoracic 139 (32%), lumbar 91 (21%) AIS: __ Etiology: 412 acquired (94%), congenital 26 (6%) Age: mean 42, 10-80 years Duration: Females: mean 11, 0-59 years Males: mean 13, 1-61 years % Female: 29.5% BMD: __ Osteoporosis: 9 osteoporotic Family History of Fractures: 283 No (65%); 100 Yes (23%); 41 Don't Know (9%) Able-bodied group N: 654 Age: mean 43, range 19-93 % Female: 49.2% BMD: __ Osteoporosis: 6 osteoporotic Family History of Fractures: 347 No (53%); 229 Yes (35%); 78 Don't Know (12%)	Objective: To evaluate risk factors and fracture rates in SCI patients. Comparing: Participants with SCI and randomly selected normal controls on risk factors and fracture rates.	Timeline: unclear Data Source: Members of the Danish Paraplegic Association and randomly selected normal controls; demographic, lifestyle and clinical status questionnaire. Clinical Risk Factors Examined: age, gender, smoking, use of corticosteroids, family fracture history, family/personal osteoporosis history, location and cause of fracture	Significant Risk Factors: 1. Family history of fractures: (RR 1.5, p<0.02) 2. Location of SCI (RR 1.9, p<0.002 – Lumbar higher risk) 3. Crude fracture rate: 2% per year in patients and 1% per year in controls (RR 2.0, p<0.001). Non-Significant Risk Factors 1. Family History of Osteoporosis 2. Corticosteroid use 3. Frequency of Outdoor activities 4. Work 5. Sports 6. Mobility Smoking
Vlychou, 2003 Case-Control Study Greece	Paraplegic group N: 57 Level: T1-T6: 19 (33.3%), T7-L2: 38 (66.7%) AIS: Frankel: 35 A, 22 B/C/D Etiology: traumatic Age: Males: mean 39.3, 21-66 years Females: mean 37.8, 22-47 years Duration: mean 7.3 ± 3.6 years % Female: 42.1% Mean Femoral Neck (g/cm2):	Objective: To study BMD measurements (using DXA – Norland XR 36) in the forearm, leg and hip among people with paraplegia and able-bodied matched controls.	Timeline: unclear Data Source: Clinical examination using DXA. Clinical Risk Factors Examined: Age, sex, height, weight, etiology of injury, SCI duration, physiotherapy, and standing status	Significant Risk Factors: 1. Reduction of BMD of femoral neck (p<0.001) in male and female paraplegics compared to control Non-Significant Risk Factors 1. SCI severity: Complete vs. incomplete lesions 2. SCI level (lesion above or below T6) 3. Standing and rehabilitation programs 4. SCI duration

Vlychou, 2003 Case-Control Study Greece	Males: 0.752 ± 0.157 Females: 0.688 ± 0.157 Mean Z-score at Femoral Neck: Males: -1.483 ± 1.209 Women: -1.454 ± 1.223 Osteoporosis: __ Able-bodied Control group N: 36 Age: Males: mean 39.9, 23-66 years Females: mean 37.1, 25-47 years % Female: 44.4% Mean Femoral neck aBMD (g/cm²): Males: 0.981 ± 0.139 Females: 0.90 ± 0.184 Mean Femoral neck Z-score: Males: 0.335 ± 1.067 Females: 0.328 ± 1.486 Osteoporosis: __	Comparing: paraplegic patients and able-bodied controls on BMD measurements and clinical parameters (level of injury, physiotherapy and therapeutic standing)		
Wood, 2001 Cross-sectional Study United Kingdom	N: 22 Level: T3-T12; paraplegic; complete AIS: __ Etiology: __ Age: mean 36.4 ± 10 years Duration: mean 7.6 ± 6.8 years % Female: 0% Mean Femoral neck Z-score: 18 participants Z-score < -1, 5 participants Z-score < -2 Inconsistency with sample size numbers in relation to Z-scores	Objective: Investigate potential correlation between bone loss and age, SCI level, SCI duration. Comparing: Demographics and clinical characteristics in SCI participants.	Timeline: unclear Data Source: Clinical examination using DXA (femoral neck). Clinical Risk Factors Examined: age, SCI level, SCI duration	Significant Risk Factors: None reported Non-Significant Risk Factors: 1. Age 2. Lesion level 3. SCI duration
Yilmaz, 2007 Cross-sectional Study Turkey	All N: 30 Level: 19 (63.3%) paraplegic, 11 (36.7%) tetraplegic; 100% complete AIS: A-B Etiology: traumatic Age: mean 32 ± 10 years Duration: mean 30.2 months % Female: 0% Osteoporosis: 8 osteoporotic, 13 osteopenic AIS A N: 22 Age: mean 31.86 ± 10.78 years Mean aBMD (g/cm²): Femur neck: 0.88 ± 0.21 Ward's triangle: 0.83 ± 0.23 Trochanter: 0.71 ± 0.18 Femur shaft: 1.03 ± 0.24 Total femur: 0.88 ± 0.1	Objective: Investigate relationship between basal metabolic rate (BMR), aBMD, and SCI level. Comparing: Clinical characteristics; AIS A vs. AIS B; tetraplegic vs. paraplegic.	Timeline: unclear Data Source: Clinical examination using DXA (femur neck, Ward's triangle, trochanter, femur shaft, total femur), indirect calorimetry. Clinical Risk Factors Examined: Basal metabolic rate (BMR), lean-tissue mass, SCI level	Significant Risk Factors: 1. BMR: correlated significantly with hip aBMD a. Femur neck ($r=0.44$, $p=0.01$) b. Trochanter ($r=0.43$, $p=0.02$) c. Femur shaft ($r=0.37$, $p=0.04$) d. Total femur ($r=0.41$, $p=0.02$) e. Stronger correlation tetraplegics vs paraplegics: i. Femur neck: $r=0.67$ $p=0.02$ vs. $r=0.39$, $p=0.16$, respectively ii. Trochanter: $r=0.62$, $p=0.04$ vs. $r=0.32$ $p=0.17$, respectively iii. respectively iv. Femur Shaft: $r=0.65$, $p=0.02$ vs. $r=0.29$ $p=0.22$, respectively Non-Significant Risk Factors: 1. SCI level: Paraplegia vs. tetraplegia aBMD 2. Lean-tissue mass 3. AIS A-B

	AIS B N: 8 Age: mean 32.50 ± 10.55 years Mean aBMD (g/cm2): Femur neck: 0.81 ± 0.20 Ward's triangle: 0.75 ± 0.21 Trochanter: 0.68 ± 0.16 Femur shaft: 0.93 ± 0.24 Total femur: 0.82 ± 0.20 Tetraplegic N: 11 Age: mean 28.6 ± 10.4 years Mean aBMD (g/cm2): Femur neck: 0.88 ± 0.14 Ward's triangle: 0.84 ± 0.14 Trochanter: 0.69 ± 0.12 Femur shaft: 1.01 ± 0.19 Total femur: 0.86 ± 0.14 Paraplegic N: 19 Age: mean 34.0 ± 10.3 years Mean aBMD (g/cm2): Femur neck: 0.85 ± 0.24 Ward's triangle: 0.79 ± 0.26 Trochanter: 0.70 ± 0.20 Femur shaft: 1.00 ± 0.27 Total femur: 0.86 ± 0.22			
Zehnder, 2004 Cross-sectional Study Switzerland	All N: 100 (98 included) Level: T1-5 (21%), T6-T10 (44%), T11-L3 (35%); paraplegic AIS: Frankel: 94 A, 6 B Etiology: traumatic Age: mean 38.0 SEM 0.97, 19.3-59.9 years Duration: mean 10.4 SEM 9.5, 0.1-29.5 years % Female: 0% Osteoporosis: __ Stratum I (<1 year SCI duration) N: 16 Mean aBMD (g/cm2): Femoral neck: 0.887 ± 0.029 Tibial epiphysis: 0.870 ± 0.028 Tibial diaphysis: 1.422 ± 0.031 Mean Z-score: Femoral neck: -0.03 ± 0.25 Tibial epiphysis: -0.34 ± 0.22 Tibial diaphysis: 0.44 ± 0.27 Fracture Incidence (%/year): 1	Objective: Document fracture history, BMD, biomarker parameters in SCI patients. Comparing: Demographics within SCI duration groups (Stratum I vs. Stratum II vs. Stratum III vs. Stratum IV).	Timeline: November 1997 to June 1999 Data Source: Clinical examination using DXA (femoral neck, tibial epiphysis, tibial diaphysis) blood and urine analysis, nutrition and lifestyle questionnaire. Clinical Risk Factors Examined: fracture history, SCI duration, age, smoking history, alcohol consumption, physical activity levels, spasticity, calcium intake	Significant Risk Factors: - SCI duration: - Fracture participants (n=15) had greater SCI duration (15.7 ± 1.9 vs 9.3 ± 0.8 years, p<0.01) than non-fracture participants. - aBMD decreased with increased SCI duration at all sites (all r=0.49-0.78, p<0.0001). - Bone reabsorption markers (D-pyr/Cr ratio) elevated in 50% and 30% stratum II and strata III-IV, respectively. - Decreased bone formation markers (calcium and OC) with increased SCI duration (r=0.34, r=0.37, respectively, both p<0.001) - Age: Bone formation markers (Ca2 and OC) decreased significantly with age (r=0.34 and 0.44, respectively; both p<0.001) - Smoking status: Smokers (n=47) had lower aBMD Z-scores than non-smokers. - Femoral neck: -1.7 ± 0.18 vs. -1.1 ± 0.18, p<0.05 - Tibial epiphysis: -3.8 ± 0.23 vs. -2.9 ± 0.23, p<0.01 - Tibial diaphysis: -1.8 ± 0.26 vs. -1.1 ± 0.23, p<0.05 Non-Significant Risk Factors:

	Stratum II (1-9 years SCI duration) N: 38 Mean aBMD (g/cm²): Femoral neck: 0.661 ± 0.019 Tibial epiphysis: 0.446 ± 0.016 Tibial diaphysis: 1.221 ± 0.027 Mean Z-score: Femoral neck: -1.65 ± 0.17 Tibial epiphysis: -3.81 ± 0.13 Tibial diaphysis: -1.29 ± 0.23 Fracture Incidence (%/year): 1.3 Stratum III (10-19 years SCI duration) N: 31 Mean aBMD (g/cm²): Femoral neck: 0.634 ± 0.029 Tibial epiphysis: 0.407 ± 0.026 Tibial diaphysis: 1.091 ± 0.037 Mean Z-score: Femoral neck: -1.76 ± 0.25 Tibial epiphysis: -4.00 ± 0.21 Tibial diaphysis: -2.38 ± 0.32 Fracture Incidence (%/year): 3.4 Stratum IV (20-29 years SCI duration) N: 13 Mean aBMD (g/cm²): Femoral neck: 0.602 ± 0.033 Tibial epiphysis: 0.391 ± 0.028 Tibial diaphysis: 1.076 ± 0.045 Mean Z-score: Femoral neck: -1.76 ± 0.28 Tibial epiphysis: -4.12 ± 0.24 Tibial diaphysis: -2.49 ± 0.39 Fracture Incidence (%/year): 4.6			1. Physical activity 2. Alcohol consumption 3. Calcium intake 4. Spasticity
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Section 2.0 – Evidence Tables for Laboratory Screening

Evidence Table 2A: Current Guideline Recommendations for Laboratory Workup of Bone Health in Able-Bodied Population

Guideline Group	Guideline and Year	Recommendations
Camacho, 2016 American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE)	AACE and ACE Clinical Practice Guidelines For The Diagnosis and Treatment of Postmenopausal Osteoporosis 2016	“Consider using bone turnover markers (BTMs) in the initial evaluation and follow-up of osteoporosis patients. Elevated levels can predict more rapid rates of bone loss and higher fracture risk (Grade B; BEL 1, downgraded based on expert consensus).” “Measure serum 25-hydroxyvitamin D (25[OH] D) in patients who are at risk for vitamin D insufficiency, particularly those with osteoporosis (Grade B; BEL 2).”

Cosman, 2014 National Osteoporosis Foundation (NOF)	Clinician's Guide to Prevention and Treatment of Osteoporosis 2014	"Under Diagnostic Assessment: Biochemical markers of bone turnover can aid in risk assessment and serve as an additional monitoring tool when treatment is initiated."
Gordon, 2017 Journal of Clinical Endocrinology and Metabolism	Functional Hypothalamic Amenorrhea: An Endocrine Society Clinical Practice Guideline 2017	"In adolescents and women with suspected FHA, we recommend obtaining the following screening laboratory tests: b-human chorionic gonadotropin, complete blood count, electrolytes, glucose, bicarbonate, blood urea nitrogen, creatinine, liver panel, and (when appropriate) sedimentation rate and/or C-reactive protein levels." "As part of an initial endocrine evaluation for patients with FHA, we recommend obtaining the following laboratory tests: serum thyroid-stimulating hormone (TSH), free thyroxine (T4), prolactin, luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E2), and antiMüllerian hormone (AMH). Clinicians should obtain total testosterone and dehydroepiandrosterone sulfate (DHEA-S) levels in patients with clinical hyperandrogenism and 8 AM 17-hydroxyprogesterone levels if clinicians suspect late onset congenital adrenal hyperplasia (CAH)" "Many studies have reported hormonal alterations among amenorrheic hyperexercisers compared with eumenorrheic hyperexercisers and nonexercisers, including: higher cortisol and ghrelin and lower leptin secretion accompanying lower LH secretion; a blunted elevation in FSH during the luteal-follicular transition, which may predispose to luteal phase defects (i.e., luteal phase deficiency in progesterone secretion) and abnormalities in peptide YY and other adipokines" "Patients with FHA have characteristically low or low normal LH, normal FSH concentrations (which are usually higher than LH concentrations), E2, 50 pg/mL, and progesterone, 1 ng/mL; the acute gonadotropin response to GnRH stimulation is preserved (defined as a twofold to threefold rise in LH and FSH compared with baseline levels)." "In the absence of signs of androgen excess, measuring FSH, LH, prolactin, TSH, and free T4 will generally provide sufficient information to rule out organic causes of amenorrhea"
NOGG, 2017 National Osteoporosis Guideline Group	NOGG 2017: Clinical Guideline for the Prevention and Treatment of Osteoporosis 2017	"Procedures proposed in the investigation of osteoporosis: • Blood cell count, sedimentation rate or C-reactive protein. Serum calcium, albumin, creatinine, phosphate, alkaline phosphatase and liver transaminases" "Other procedures, if indicated • Serum protein immunoelectrophoresis and urinary Bence Jones proteins • Serum 25-hydroxyvitamin D • Plasma parathyroid hormone • Serum testosterone, sex hormone binding globulin, follicle stimulating hormone, luteinizing hormone • Serum prolactin • Markers of bone turnover • Urinary calcium excretion 24 hour urinary free cortisol/overnight dexamethasone suppression test"
Papaioannou, 2010 Canadian Medical Association Journal	Clinical Practice Guidelines for the Diagnosis and Management Of Osteoporosis in Canada: Summary 2010	"Perform additional biochemical testing [they do not identify specifics] to rule out secondary causes of osteoporosis in selected patients, on the basis of the clinical assessment [Grade D]." "Measure serum level of 25-hydroxyvitamin D in individuals who will receive pharmacologic therapy for osteoporosis, those who have sustained recurrent fractures or have bone loss despite osteoporosis treatment, and those with comorbid conditions that affect absorption or action of vitamin D [Grade D]." "Serum 25-hydroxyvitamin D should not be measured in healthy adults at low risk of vitamin D deficiency, i.e., without osteoporosis or conditions affecting the absorption or action of vitamin D [Grade D]."

RACGP, 2017 Royal Australian College of General Practitioners and	Osteoporosis prevention, diagnosis and management in postmenopausal women and men over 50 years of age; 2nd Edition	“Relevant blood and urine studies should be obtained prior to initiating therapy if the medical history and/or clinical examination is compatible with secondary osteoporosis, or the DXA Z-score is ≤ -2.0.” “Serum 25-OH D levels should be checked, optimised and maintained during osteoporosis therapy.”
Osteoporosis Australia	2017	“Re-measure serum 25-OH D concentrations after three months of treatment to ensure levels 50–75 nmol/L.” ““The International Osteoporosis Foundation and International Federation of Clinical Chemistry and Laboratory Medicine recommend one serum bone formation marker (procollagen type I amino-terminal propeptide, or PINP) and one bone resorption marker (C-terminal telopeptide, or CTX) to be used as reference markers. These should be measured by standardised assays in observational and intervention studies in order to compare the performance of alternatives and to enlarge the international experience of the application of markers to clinical medicine.”
Watts, 2012 The Endocrine Society’s Clinical Guidelines Subcommittee and Clinical Affairs Core Committee	Osteoporosis in Men: An Endocrine Society Clinical Practice Guideline 2012	“We suggest measuring serum calcium, phosphate, creatinine (with estimated glomerular filtration rate), alkaline phosphatase, liver function, 25-hydroxyvitamin D [25(OH)D], total testosterone, complete blood count, and 24-h urinary calcium (creatinine and sodium) excretion in men being evaluated for osteoporosis or considered for pharmacological treatment with bone-active agents. (Weak Recommendation; Low Quality of Evidence)” “If history or physical examination suggest a specific cause of osteoporosis, further testing should be done. Depending on the findings of the history and physical examination, such testing may include (but is not limited to) calculated free or bioavailable testosterone (using measurements of SHBG), serum protein electrophoresis with free κ and λ light chains and/or urine protein electrophoresis, tissue transglutaminase antibodies (for celiac disease), thyroid function tests, and PTH levels. (Weak Recommendation; Low Quality of Evidence)” “We suggest that clinicians consider measuring a bone turnover marker (BTM) at 3–6 months after initiation of treatment using a bone resorption marker [such as serum C-telopeptide of type I collagen (CTX) or serum or urine N-telopeptide of type I collagen (NTX)] for antiresorptive therapy and a bone formation marker [such as serum procollagen I N-propeptide (PINP)] for anabolic therapy. (Weak Recommendation; Moderate Quality of Evidence)”

Section 4.0 - pQCT and QCT

Evidence Table 4A: pQCT and QCT Diagnosis of Lower Extremity Osteoporosis

Author, Year Study Design Setting	Population Characteristics Sample Size Injury Level AIS Score Injury Etiology Mean Age & Range Duration of Injury % Female Baseline Bone Characteristics Osteoporotic Status	Objective or Intervention Comparison Groups	DXA Model & Software (p)QCT Model (p)QCT Scanner Method (p)QCT Imaging Acquisition Measure Sites Timeline of DXA and (p)QCT Scans Outcomes Precision Measures	Relevant Results
Dionyssiotis, 2009 Cross-sectional USA	All SCI N: 30 Level: paraplegic; complete AIS: ____ Etiology: ____ Osteoporosis: ____ High Level SCI Group N: 15	Objective: Correlate DXA derived bone measurements to QCT of matched regions Comparing: paraplegic groups vs. controls; BMC and bone stress-strain index vs. demographic factors	DXA Model: DEXA XR-36 pQCT Model: Stratec XCT-3000 pQCT Method: ____ DXA Sites: total lower-limb pQCT Sites: 14% and 38% left tibia	Compared to the control group: 1. SSI at 14% tibia was 14.45% less for the high level group and 24.66% less for the low level group (both $p=0.001$). 2. SSI at 38% tibia was 19.08% less for the high level group and 17.16% less for the low level group (both $p=0.001$). 3. BMC was reduced for the both paraplegic groups ($p<0.001$).

	Level: T4-T7 Age: mean 32.88 + 15.6 years Duration: mean 5.97 + 5.9 years % Female: 0% Lower Limb BMC: mean 898.14 + 202.88 g Low Level SCI Group N: 15 Level: T8 – T12 Age: mean 39.47 + 13.81 years Duration: mean 5.65 + 5.8 years % Female: 0% Lower Limb BMC: mean 873.60 + 155.21 g Control Group Defined as able bodied individuals with matched age, weight and height. N: 33 Age: mean 37 + 19 years Lower Limb BMC: mean 1,213.84 + 149.37 g		Timeline: __ Outcomes: DXA based lower-limb BMC and QCT based bone stress-strain index (SSI)	Additional Correlations: 1. SSI at 14% tibia was negatively correlated with the low level group ($r=-0.473$; $p=0.041$). 2. SSI at 38% was negatively correlated with duration of injury in the low level group ($r=-0.475$; $p=0.04$). 3. Mean difference between SSI at 14% and 38% of the tibia was correlated with duration of injury for the low level group ($r=0.534$; $p=0.027$). 4. BMC was negatively correlated with duration of injury for high level group ($r=-0.658$; $p=0.006$).
Lala, 2014 Cross-Sectional	All N: 70 Level: 23 motor complete paraplegics, 11 motor incomplete paraplegics, 22 motor	Objective: Examine if DXA-based aBMD or pQCT-based bone geometry of the tibia are associated with chronic	DXA Model: Hologic 4500A; Hologic commercial software pQCT Model: Stratec XCT-2000; version 6.00	pQCT Results (Fracture Group vs. None Fracture group) vBMDtrab (84.4 + 33.3 vs. 145.7 + 56.3 mg/cm³; $p<0.001$)
Canada	complete tetraplegics, 14 motor incomplete tetraplegics AIS: __ Etiology: __ Osteoporosis: __ Fracture Group N: 19 Age: mean 48.9 + 10.6 years Duration: mean 19.4 + 11.8 years % Female: 32% Mean aBMD (g/cm²) Total Hip: 0.730 + 0.19 Femoral Neck: 0.689 + 0.13 Distal Femur: 0.454 + 0.11 Proximal Tibia: 0.371 + 0.10 None Fracture Group N: 51 Age: mean 48.8 + 11.9 years Duration: mean 14.0 + 8.9 years % Female: 27% Mean aBMD (g/cm²) Total Hip: 0.769 + 0.17 Femoral Neck: 0.595 + 0.14 Distal Femur: 0.667 + 0.20 Proximal Tibia: 0.541 + 0.16	SCI lower extremity fragility fractures. Comparing: DXA based knee aBMD and pQCT-based bone geometry vs. fracture status	software pQCT Method: __ pQCT Imaging: 0.2mm voxel size at 4% tibia, 0.5mm voxel size at 66% tibia; 2.5 mm slice thickness; vBMDtrab assessed using contour mode 3 and peel mode 2 with an outer threshold of 130 mg/cm³ and an inner threshold of 400mg/cm³ and all other parameters were assessed using contour mode 1 and a threshold of 710 mg/cm³ DXA Sites: left total hip, left femoral neck, right distal femur and right proximal tibia pQCT Sites: 4% and 66% tibia Timeline: __ Outcomes: fracture status, aBMD, and vBMDtrab	Increased risk of fractures associated with each SD decrease in: 1. DXA-based and pQCT-based measures of BMD and geometry except for CSMI (OR=2.0, 95%CI [1.0, 4.8], $p=0.07$) 2. Distal femur aBMD, after adjusting for motor complete injury (OR=4.9; 95%CI [1.7, 17.5]) 3. Proximal tibia aBMD after adjusting for motor complete injury (OR=6.1; 95%CI [2.1, 23.6]) 4. vBMDtrab (OR=6.5; 95%CI [1.9, 32.9])

McPherson, 2014 Methodological Validation	Acute SCI N: 12 Level: 66.7% cervical, 33.3% thoracic AIS: ____ Etiology: ____	Objective: Correlate DXA derived bone measurements to QCT of matched regions Comparing: DXA based knee	DXA Model: Hologic QDR45400A; APEX Software QCT Model: Sensation 64 Cardiac scanner	Pearson product moment correlation DXA aBMD and QCT vBMD values: 1. Distal femur epiphysis (r=0.955) 2. Distal femur metaphysis (r=0.945) 3. Proximal tibia epiphysis (r=0.934)
USA	Age: mean 28.2 + 13.0 years Duration: mean 2.1 + 0.7 months % Female: 33.3% Mean aBMD (g/cm ²) 0 -10% Femur: 1.255 10 – 20% Femur: 0.927 0 -10% Tibia: 0.944 Osteoporosis: ____ Chronic SCI N: 34 Level: 26.5% cervical, 70.6% thoracic, 2.9% lumbar AIS: ____ Etiology: ____ Age: mean 41.9 + 12.2 years Duration: mean 196.9 + 111.4 months % Female: 21.6% Mean aBMD (g/cm ²) 0 -10% Femur: 0.606 10 – 20% Femur: 0.460 0 -10% Tibia: 0.458 Osteoporosis: ____	aBMD vs. QCT based knee vBMD	QCT Method: 120 kVp; 280 mA; synchronous calibration; image alignment using Mimics software QCT Imaging: 0.352 mm pixel resolution; 1mm slice thickness Sites: distal femoral epiphysis (0 -10% femur), distal femoral metaphysis (10 – 20% femur), and proximal tibial epiphysis (0 -10% tibia). Timeline: QCT scan performed within 2 weeks of DXA scan Outcomes: aBMD and vBMD Precision Measures: For knee DXA protocol for the acute SCI group, average RMS-CV% values were 1.70%, 1.39% and 1.66% for the distal femur epiphysis, distal femur metaphysis and proximal tibia epiphysis. For the chronic SCI group, average RMS-CV% values for the same regions were 3.12%, 4.70% and 3.40% respectively. ICC for both groups was 0.97.	
Tan, 2014 Cross-sectional USA	N: 27 Level: 19 paraplegics, 8 tetraplegics; 22 motor complete AIS: ____ Etiology: ____ Age: mean 40.7 + 11.5 years Duration: mean 13.2 + 11.7 years Mean aBMD (g/cm ²) Total Hip: 0.788 ± 0.232 Femur Neck: 0.809 ± 0.236 Distal Femur: 0.729 ± 0.262 Proximal Tibia: 0.738 ± 0.287 Osteoporosis: 10 had normal aBMD, 2 had osteopenia and 15 had osteoporosis Post-SCI osteoporotic fracture: 21 no, 6 yes	Objective: Correlate DXA derived bone measurements to QCT of matched regions. Comparing: DXA-based aBMD vs. QCT-based bone strength vs. demographic factors	DXA Model: GE Healthcare iDXA 5th generation; enCore configuration V12.3 software QCT Model: Siemens Definition Flash (n= 20) or GE Lightspeed Pro (n= 7) Siemens QCT Method: 120 kV; 80 mA GE QCT Method: 120 kV; 50 mA QCT Imaging: 10mm slice thickness DXA Sites: proximal tibia and distal femur QCT Site: distal femur (single slice) Timeline: time between DXA-scan and QCT scan unclear Outcomes: DXA-based aBMD and QCT- based bone strength of femur (axial stiffness and maximal load to fracture) Left and right femoral axial stiffness and maximal load were combined because of close correlation (r=0.70 for axial stiffness and r=0.83 for maximal load, p<0.0001 for both)	1. Distal femur axial stiffness correlated with aBMD for: a. Distal Femur (r=0.58, p=0.002) b. Proximal Tibia (r=0.52, p=0.007) c. Femur Neck (r=0.40, p=0.04) d. Total Hip (r=0.35, p=0.07) 2. Distal femur maximal load was correlated with aBMD for: a. Distal Femur (r=0.83, p<0.0001) b. Proximal Tibia (r=0.76, p<0.0001) c. Femur Neck (r=0.57, p=0.001) d. Total Hip (r = 0.59, p=0.001) 3. Compared to individuals without osteoporotic fractures, those who had fractures had lower distal femur axial stiffness (99.51 ± 56.3 vs. 160.59 ± 49.0 MPa; p=0.01) and maximal load (38.39 ± 14.6 vs. 91.11 ± 40.8 kg; p=0.005).

Evidence Table 4B-1: Observational and Interventional Bone studies using pQCT in ACUTE stage of SCI (duration <2 yrs)

Author, Year Study Design Setting	Population Characteristics Sample Size Injury Level AIS Score Injury Etiology Mean Age & Range Duration of Injury % Female Baseline Bone Characteristics Osteoporotic Status	Objective or Intervention Comparison Groups	DXA Model & Software (p)QCT Model (p)QCT Scanner Method (p)QCT Imaging Acquisition Measure Sites Timeline of DXA and (p)QCT Scans Outcomes Precision Measures	Relevant Results
Coupaud, 2012 Longitudinal UK	SCI N: 6 Injury Level: S1 - C4 S2 - T9 S3 - C4/5 S4 - T3 S5 - T4 S6 - T6 AIS Score: A & B Injury Etiology: traumatic Age: mean 28.5, range 17-72 years Duration of Injury: < 5 weeks - 12 months % Female: 0% BMD Distal Tibia: BMDtrab = 272.11 (33.62) BMDtot = 331.75 (24.49) BMC = 4.39 (0.60) BMD Proximal Tibia: BMDtrab = 191.79 (31.57) BMDtot = 250.46 (29.13) BMC = 7.57 (1.16) BMD Distal Femur: BMDtrab - 256.99 (31.55) BMDtot - 277.75 (23.41) BMC - 11.41 (1.23) Osteoporotic Status: __	Objective or Intervention: Systematic evaluation of bone status in the early stages of SCI to identify fast bone losers. Comparison Groups: Chronic SCI & Able-bodied reference values taken from Eser et al. 2004 Complications: __	DXA Model & Software: __ (p)QCT Model: XCT550, Stratec Medinzintechnik, Pforzheim, Germany (p)QCT Scanner Method: At 4% total bone length; slice thickness was set at 2 mm and voxel size at 0.5 mm in the tibia and radius and 0.3 mm in the femur. (p)QCT Imaging Acquisition: Contour algorithm used (threshold 180 mg cm⁻³ in the distal tibia, 150 mg cm⁻³ in the proximal tibia, 130 mg cm⁻³ in the distal femur and 150 mg cm⁻³ in the distal radius) to find the periosteal surface of the epiphysis for calculation of BMC, total bone CSA and BMDtrab. For BMDtrab calculations, concentric pixel layers were peeled off from the perimeter until the central 45% area remained. Measure Sites: Distal Tibia, Proximal Tibia, Distal Femur Timeline of (p)QCT Scans: Baseline scans within 5 weeks of injury; follow up scans at 4, 8 and 12 months post-injury Outcomes: BMD and BMC measured at fracture-prone sites in the tibia and femur. Patient-specific predictions of expected rates of bone loss produced according to patients' measured values at baseline Precision Measures: Quality assurance scans performed using manufacturer's phantom; Wilcoxon Signed Rank Test; standardised residuals calculated and summed for each subject (compared to a chi-squared distribution with three degrees of freedom).	Distal Tibia: BMDtrab - 160.53 (84.18) BMDtot - 215.40 (68.03) BMC - 2.78 (0.78) Proximal Tibia: BMDtrab - 108.09 (37.73) BMDtot - 151.93 (33.32) BMC - 4.78 (0.78) Distal Femur: BMDtrab - 185.91 (39.58) BMDtot - 202.44 (27.34) BMC - 8.02 (0.95) Distal tibia: All changes statistically significant - p values range: 0.028-0.043) Proximal tibia: Statistically significant (except between 8 and 12 months for BMDtrab and BMDtot) - p = 0.080 Distal femur: Statistically significant (except BMDtrab between 4 and 8 months post-injury, BMDtot between 8 and 12 months post-injury, and BMC between 8 and 12 months post-injury) - p = 0.080 At 12 months, values remained substantially higher than in people with long-term motor-complete SCI. • Taken from Eser et al. 2004

Coupaud et al. 2015 Longitudinal Scotland	N: 26 (complete data available over the 12 months for only 19 for femur participants and 17 for tibia participants) Level: 12 paraplegic, 14 tetraplegic AIS: __ Etiology: traumatic Age: mean 38.7 ± 19.3 years (range 16-76) Duration: acute % Female: 20% Osteoporosis: __	Objective: Using repeat pQCT scans at 4, 8 and 12 months post-injury, changes in BMC, bone mineral density (BMD) and cross-sectional area (CSA) of the bone were quantified. Comparing: Unilateral scans of the tibia and femur provided separate estimates of trabecular and cortical bone parameters in the epiphyses and diaphysis respectively. Complications Missing data resulted from scanning complications; two 4% proximal tibia were discarded due to excessive movement artefact from spasm	Timeline: Scans were carried out within 5 weeks post-injury, and repeated at 4, 8 and 12 months post-injury. Data Source: peripheral Quantitative Computed Tomography (pQCT) scans (XCT 3000, Stratec Medizintechnik, Pforzheim, Germany).	1. There was no significant effect of gender or age on key outcome measures. 2. For epiphyseal sites, within-subject analyses (with simple contrasts) revealed a statistically-significant effect of time since injury (TSI) on trabecular and total BMD in both the tibia and femur (p-values: 0.002–0.043). Proximal tibia 96% N = 17 • Total BMD (mg/cm3) • Baseline - 251.16 (32.94); • 12 months post-injury - 185.23 (43.47) (p<0.001) • Trabecular BMD (mg/cm3) • Baseline - 175.34 (39.13) • 12months post-injury 136.50 (37.96) (p<0.001) • Distal femur 4% N = 19 • Total BMD (mg/cm3) Baseline - 286.27 (26.40) • 12 months post-injury 237.11 (39.66) (p<0.001) • Trabecular BMD (mg/cm3) 262.37 (31.39) • 12 months post-injury - 221.49 (41.93) (p<0.001)
de Bruin, 1999 RCT Switzerland PEdro=6	All N: 19 Level: __ AIS: __ Etiology: traumatic Age: __ Duration: __ % Female: 0% Ambulation: __ BMD: __ Osteoporosis: __ Immobilization Group N: 4 Level: 2 cervical, 1 thoracic, 1 lumbar AIS: 1 A, 2 B, 1 C Age: mean 27.5, 21 – 33 years Standing Group N: 5 Level: thoracic; AIS: 4 A, 1 B Etiology: __ Age: mean 35.2, range 25 - 48 years Duration: mean 2, 1-3 weeks	Intervention: Standing/Walking for 25 weeks. Immobilization Group: 0 – 5 hour loading exercises with standing frame per week Standing Group: 5+ hour of standing exercises per week Walking Group: 5+ hours of standing and treadmill walking Comparing: before vs. after; each intervention group	Timeline: follow ups after 5, 9, 13, 17, 21, and 25 weeks post injury Data Source: clinical examination using pQCT pQCT Model: Densi-scan 2000 Outcomes: trabecular vBMD, cortical vBMD	1. Trabecular BMD of the left tibia was significantly lower for the immobilization group compared to the standing or walking groups. No significant difference between standing or walking group for trabecular vBMD 2. No significant difference groups for the cortical vBMD.

	Walking Group N: 4 Level: 3 cervical, 1 thoracic AIS: 3 C, 1 D Age: mean 34.8, 22 - 53 years Duration: mean 3.3, 2 - 4 weeks Control defined as no intervention. N: 6 Level: 2 cervical, 4 thoracic AIS: 3 A, 2 B, 1 D Etiology: __ Age: mean 33.7, 19 - 59 years Duration: 5 weeks % Female: __ Ambulation: __ BMD: __ Osteoporosis: __			
de Bruin, 2000 Longitudinal Switzerland	SCI N: 12 (10 completed) Injury Level: S1 - T8 S2 - T1 S3 - T9 S4 - T11 S5 - T5 S6 - T11 S7 - L5 S8 - T12 S9 - C6 S10 - T11 AIS Score: __ Injury Etiology: traumatic Age: mean 40.9 + 19.7 years Duration of Injury: __ % Female: __ Baseline Bone Characteristics: __ Osteoporotic Status: __	Objective or Intervention: The aim of this study was to find an answer to the following two questions: First, do changes in BMD following an SCI reach a 'steady state' after more than 2 years post injury? Second, are there high interindividual variations of change in BMD following an SCI? Comparison Groups: __ Complications: __	DXA Model & Software: __ (p)QCT Model: Densiscan 1000 (p)QCT Scanner Method: __ (p)QCT Imaging Acquisition: __ Measure Sites: Distal Tibia Timeline of DXA and (p)QCT Scans The first pQCT bone measurements were performed at week 5 after accident (t1), the last measurement 40.875.9 months after the first measurement (t2) Outcomes: __ Precision Measures: To ensure that the CT scans were always made at the same angle relative to the bone axis the extremity involved was measured in an anatomically formed radiolucent cast	Results only presented as a % change from T1-T2 Tibia % change Trabecular Bone: S1 - 83.5 S2 - 71 S3 - 56.6 S4 - 50.9 S5 - 57.5 S6 - 37 S7 - 12.5 S8 - 13.7 S9 - 9.8 S10 - 7.8
Dudley-Javoroski, 2012 Longitudinal (intervention) USA	All N: 42 Etiology: __ BMD: __ Osteoporosis: __ High Dose Group N: 7 Level: 6 thoracic, 1 cervical AIS: 7 A Age: mean 25.7, 16 - 37 years Duration: mean 0.8, 0.22-2.05 years	Intervention: 3 doses of bone compressive loads 5x/week for over 3 years. Untrained: 0% body weight load Low Dose: passive standing with 40% body weight load for 30 minutes	Timeline: Follow ups were 1-6 times over 3-year period. Time Bins (Post SCI): 0 - 0.25 years 0.25 - 0.50 years 0.50 - 0.75 years 0.75 - 1 years 1 - 1.5 years 1.5 - 2 years >2 years	Overall: - No significant difference between the low dose and untrained groups. Distal Femur Results: - High dose group BMD exceeded BMD of the untrained group (p=0.003) and low dose group (p=0.019). - Slope of BMD decline over time for untrained/low dose groups (-38.776 mg-cm³/year) were 3 times greater than the high dose group (-11.970 mg-cm³/year).

	Duration: mean 0.8, 0.22-2.05 years % Female: 14.3% Low Dose Group N: 5 Level: 5 thoracic AIS: 4 A 1 B Age: mean 39.6, 34 - 44 years Duration: mean 0.5, 0.21 – 0.68 years % Female: 0% Untrained N: 16 Age: mean 38.9, 18 - 64 years Duration: mean 7.4, 0.19 - 24.23 years % Female: 18.8% Able Bodied Individuals defined as normative control. N: 14 Age: mean 30.5, range 22 - 50 years % Female: 21%	High Dose: Unilateral quadriceps FES stimulation in supported stance (150% body weight compressive load = “High Dose”) while opposite leg received 40% body weight = “Low Dose”. FES was delivered 60 100-pulse trains at 20 Hz, up to 200 mA, with 5 seconds of rest between trains. Two stimulation bouts completed each session. Comparing: before vs. after; each SCI group Complications: unclear monitoring, not reported	Data Source: clinical assessment using pQCT pQCT Model: Stratec XCT 3000 Outcomes: vBMD (proximal tibia, distal tibia and distal femur)	4. At 1 year and 3 years, BMD of untrained/ low dose groups was respectively 24.1% and 38.9% lower than the high dose group. Proximal Tibia Results: 1. Cohort dose had no significant effect on vBMD. 2. Slope of vBMD decline over time for untrained/low dose groups (-36.754 mg-cm-3/year) were 25.1% times greater than the high dose group (-29.384 mg-cm-3/year) 3. At 1 year and 3 years, BMD of untrained/ low dose groups was respectively 21.0% and 22.6% lower than the high dose group. Distal Tibia Results: 1. Cohort dose had no significant effect on vBMD. 2. Slope of BMD decline over time for untrained/low dose groups (-59.537 mg-cm-3/year) were 14.4% times lower than the high dose group (-69.261 mg-cm-3/year) 3. At 1 year and 3 years, BMD of untrained/low dose groups was respectively 5.5% lower and 37.5% greater than the high dose group.
Dudley-Javoroski, 2012 Longitudinal (intervention) USA (Continuation of Dudley-Javoroski, 2012)	FES Active Standing Group N: 7 Level: 6 thoracic, 1 cervical AIS: 7 A Etiology: ___ Age: mean 25.7, 16 - 37 years Duration: mean 0.8, 0.22-2.05 years % Female: 14.3% BMD: ___ Osteoporosis: ___ Passive Standing Group N: 5 Level: 5 thoracic AIS: 4 A 1 B Etiology: ___ Age: mean 39.6, 34 - 44 years Duration: mean 0.5, 0.21 – 0.68 years % Female: 0% BMD: ___ Osteoporosis: ___ Control defined as able-bodied individuals. N: 12 Age: mean 29.1, 22 – 48 years	Intervention: Active-resisted stance with FES of the quadriceps or passive stance 3x/week for up to 3 years. FES Active Standing: Stimulation was applied unilaterally to the quadriceps for 30 minutes at 20hz for 60 contractions at supramaximal intensity. Compression load on the femur was ~150% of body weight. Passive Standing: Compression load at all knee angles was ~40% of body weight. Comparing: before vs. after; active stance group vs. passive stance group vs. controls	Timeline: Follow ups were 1-6 times over 3-year period. Time Bins (Post SCI): 1. 0 - 0.25 years 2. 0.25 - 0.50 years 3. 0.50 - 0.75 years 4. 0.75 - 1 years 5. 1 - 1.5 years 6. 1.5 - 2 years 8. >2 years Data Source: clinical examination using pQCT pQCT Model: Stratec XCT 3000 Outcomes: trabecular vBMD (12% femur) Low dose and untrained group data was pooled.	1. At >2 years of training, distal femur trabecular BMD was higher for the active-resisted stance group than for the passive stance group (p=0.007). 2. Slope of BMD decline in the distal femur for active standing group vs. passive standing group as measured % of non-SCI BMD/year: a. Antero-lateral: -2.214 vs. -4.527 b. Anteromedial: -1.623 vs. -4.301 c. Posterolateral: -2.662 vs. -4.738 d. Posteromedial: -1.287 vs. -3.357 3. At 1.5 years, no quadrant of the femur declined 82.7% of non-SCI BMD. 4. Trabecular BMD was preferentially spared in the posterior quadrants of the femur with active-resisted stance.

	% Female: 25%	Complications: unclear monitoring, not reported		
Edwards, 2013 Longitudinal Study United States	N: 13 Level: C4-T11; 9 cervical, 4 thoracic; AIS: 4 A, 8 B, 1 C Etiology: ____ Age: mean 27.9 + 12.5 years Duration: mean 2.2 + 0.7 months % Female: 30.8% BMD: ____ Osteoporosis: ____	Objective: Quantify changes in proximal femoral strength, as determined by QCT-based fine element analysis, and aBMD, as determined by DXA, in acute SCI. Comparing: baseline vs. follow up; DXA-based aBMD vs. pQCT-based bone strength	DXA Model: Hologic QDR 4500A densitometer QCT Model: Sensation 64 Cardiac scanner QCT Method: 120 kVp; 280mAs; synchronous calibration; image alignment using Mimics software QCT Imaging: pixel resolution 0.352mm; slice thickness 1mm; 0.15g/cm ³ threshold for periosteal surface boundary; FE models generated with Matlab software; FE Models solved with ABAQUS Standard v6.1 Sites: total proximal femur and femoral neck Timeline: Follow up scan performed after Mean 3.6 months (Range 2.4 – 5.0 months) of initial scan. Two QCT scan performed Median 1 day (Range 1-14 days) of two DXA scans. Outcomes: aBMD and bone strength Precision Measures: RMS-SD for aBMD was 0.016g/cm ² for the femoral neck, and 0.008g/cm ² for the total proximal femur with corresponding LSC of 0.044g/cm ² and 0.023 g/cm ² . RMS-CV% for aBMD was 1.7% for the femoral neck, and 0.8% for the total proximal femur with corresponding LSC of 4.6% and 2.2%.	1. Mean rate of decline of aBMD were 2.0 + 1.1%/ month (p<0.001) for femoral neck and 2.2 + 0.7%/month (p<0.001) for total proximal femur. 2. Proximal femoral strength declined at a mean rate of 6.9 + 2.0 %/month (p<0.001), which was greater than the decline in femoral neck aBMD (p<0.001) and total proximal femur aBMD (p<0.001). 3. Percent changes in femoral strength were not correlated with percent changes in femoral neck aBMD (r=-0.043; N.S.) or total proximal femur aBMD (r=-0.255; N.S.).
Edwards, 2014 Longitudinal Study United States	N: 13 Level: C4-T11; 9 cervical, 4 thoracic; AIS: 4 A, 8 B, 1 C Etiology: ____ Age: mean 27.9 + 12.5 years Duration: mean 2.2 + 0.7 months % Female: 30.8% BMD: ____ Osteoporosis: ____	Objective: Quantify changes in proximal tibia and distal femur bone using QCT. Comparing: baseline vs. follow up; QCT analysis of cortical, trabecular, integral compartments of the epiphysis, metaphysis, diaphysis at the knee	DXA Model: n/a QCT Model: Sensation 64 Cardiac scanner QCT Method: 120 kVp; 280mAs; synchronous calibration; image alignment using Mimics software QCT Imaging: pixel resolution 0.352mm; slice thickness 1mm; 0.15g/cm ³ threshold for periosteal surface boundary Sites: distal femur, proximal tibia Timeline: Follow up scan performed after Mean 3.6 months (Range 2.4 – 5.0 months) of initial scan Outcomes: integral cortical, trabecular vBMD, BMC, bone volume. Change over interval period	1. Distal femur decline (% loss per month) from diaph to epiphyseal: a. Integral BMC: -1.0 to -3.0% b. Cortical BMC: -1.0 to -5.8% c. *Trabec BMC: -2.3 to 03.1% d. Integral vBMD: -0.9 to -2.8% e. Cortical vBMD: -0.5 to -0.8% f. *Trabec vBMD: -2.0 to -2.7% 2. Proximal tibia decline (% loss per month) from diaph to epiphyseal: a. Integral BMC: -0.4 to -3.6% b. Cortical BMC: -0.4 to -5.4% c. *Trabec BMC: -2.3 to -4.4% d. Integral vBMD: -0.4 to -3.4% e. Cortical vBMD: -0.3 to -0.6% f. *Trabec vBMD: -2.2 to -4.1% *Trabec compartment not quantified for diaphysis. Values reported are for metaphysis and epiphysis only

			Precision Measures: RMS CV% (Pooled Baseline & Follow-up): vBMDtot: 0.6% vBMDtrab: 1.0% Cortical BMC: 1.5%	
Frey-Rindova, 2000 Prospective Longitudinal Study Switzerland	N: 27 Level: 9 cervical, 17 thoracic, 1 lumbar AIS: __ Etiology: traumatic Age: mean 36.9 ± 13.7 years Duration: acute % Female: 6.9% Mean BMDtrab (g/cm): All subjects (n=24): 310 ± 67 Paraplegic (n=16): 314 ± 70 Tetraplegic (n=6): 299 ± 64 Active (n=13): 316 ± 72 Inactive (n=11): 302 ± 64 Mean BMDcort (g/cm3): All subjects (n=24): 924 ± 129 Paraplegic (n=18): 936 ± 136 Tetraplegic (n=6): 893 ± 113 Active (n=13): 935 ± 136 Inactive (n=11): 910 ± 126 Osteoporosis: __	Objective: Investigate the factors involved with the decrease of trabecular and BMDcort in SCI participants. Comparing: Clinical characteristics within SCI group.	Timeline: 1, 6, 12 months post- SCI Data Source: Clinical examination using pQCT (tibia) and physical examination. Clinical Risk Factors Examined: SCI duration, SCI level, spasticity, physical activity	Significant Risk Factors: 1. SCI duration: Significant decrease in bone parameters at 12 months post-SCI Tibia BMDtrab (g/cm3): All participants: 262 ± 65, p<0.05 Paraplegic: 261 ± 63, p<0.05 Tetraplegic: 265 ± 74, p<0.05 Active: 277 ± 47, p<0.05 Inactive: 249 ± 78, p<0.05 Tibia BMDcort (g/cm3): All participants: 855 ± 114, p<0.01 Paraplegic: 876 ± 120, p<0.01 Tetraplegic: 811 ± 95, p<0.01 Active: 889 ± 116, p<0.01 Inactive: 827 ± 112, p<0.01 Non-Significant Risk Factors: 1. SCI level: paraplegic vs. tetraplegic 2. Spasticity 3. Physical Activity
Giangregorio, 2005 longitudinal (intervention) Canada	N: 5 (4 completed) Level: C3-C8 AIS: 4 B, 1 C Etiology: traumatic Age: mean 29.6, 19-40 years Duration: mean 114.2, 66 - 170 days % Female: 60 % Mean aBMD Proximal Tibia: 0.961 g/cm2 Distal Femur: 1.099 g/cm2 Mean vBMD 66% Tibia: 621.8 mg/cm3 Osteoporosis: 1 had osteopenia, 4 unclear	Intervention: Body-weight supported treadmill training for 2x/week for 48 sessions during 6-8 months. Initial sessions were 5 mins and were increased gradually to 10-15 mins in all but 1 participant. Comparing: before vs. after	DXA Model: Hologic 4500A densitometer QCT Model: General Electric CTI Scanner QCT Method: 120 kV; 200 mA; BonAlyse software QCT Imaging: 512 × 512 pixel matrix; 5mm slice thickness; thresholds for outer and inner borders of bone were 280 and 70 mg/cm3 respectfully DXA Sites: proximal tibia, and distal femur QCT Sites: 66% tibia Timeline: Time between DXA-scan and pQCT scan unclear. Follow up after 6 - 8 months. Outcome: aBMD, vBMD, and pQCT-based CSA Precision Measures: RMS-CV% of < 2% for BMD and CSA measures	1. Decrease in aBMD for all participants at almost all lower limb sites after training, ranging from -1.2 to -26.7%. 2. Proximal femur aBMD, reduced by 4.3 – 22.6%. 3. No consistent changes in pQCT-based bone geometry at proximal tibia.

Shields, 2006b Prospective Controlled trial USA	N: 7 (6 complied) Level: 2 cervical, 5 thoracic; C5- T10; complete AIS: __ Etiology: __ Age: mean 29.1, range 21 – 43 years Duration: mean <4.5 months % Female: 0 % Ambulation: __ BMD: __ Osteoporosis: __	Ambulation: Untrained limb was with-in subject control. Intervention: Unilateral NMES of soleus using isometric plantar flexion protocol for ~30min/day (4 bouts with 5-min rest between bouts), 5 days/week, and for a mean of 2.42 years (Range 1.87 –3.05 years). Mean estimated compressive loads delivered to the tibia were ~1-1.5 times body weight. Comparing: trained leg vs. untrained leg Complications: unclear monitoring, not reported	Time Bins: 1. 0 to 6 weeks 2. 6 months 3. 12 months 4. 18 months 5. 24 months 6. 30 months Data Source: clinical examination using pQCT pQCT Model: Stratec XCT-20 Outcomes: cortical vBMD of the tibia at the 4%, 38%, and 66% sites and trabecular vBMD of the tibia at 4% site	1. Trabecular BMD at 4% tibia site was 40mg/cm ³ or 31% higher for the trained limb than the untrained limb. 2. No significant differences in BMDcort of the tibia at the 38% and the 66% sites.
Varzi et al. 2015 Retrospective Cohort Study Scotland	N: 25 (only 19 participants with 12 month femur data and 17 participants with 12 month tibia data) Level: Femur - Para (9), Tetra (10); Tibia – Para (8), Tetra (9) AIS: __ Femur: 14 A, 5 B; Tibia: 12 A, 5 B Etiology: all traumatic Age: median age of 33.0 (Inter-quartile range = 20.0–50.5) ranging from 16 to 76 years. Duration: 12 months % Female: 21% Osteoporosis: __	Objective: To examine 12-month total and trabecular BMD loss using multiple linear regression. Comparing: Differences in BMD bone loss at baseline vs. 12 months as measured at the distal femur and proximal tibia (%)	Timeline: Participants were scanned at the distal femur and proximal tibia using peripheral Quantitative Computed Tomography at baseline 5 weeks, 4, 8- and 12-months post-injury. Data Source: Clinical examination using XCT 3000 peripheral Quantitative Computed Tomography (pQCT) scanner (Stratec Medizintechnik GmbH). Outcomes: BMD bone loss at 12 months as measured at the distal femur and proximal tibia (%) and statistical shape modelling (SSM) of bone morphology Precision Measures	1. In the femur, there were no significant differences in bone loss (total BMD, trabecular BMD) when comparing sex, injury status (AIS and injury level) and no significant correlations with age. 2. Tetraplegics had a significantly smaller 12-month total BMD loss compared with paraplegics (-33.5% vs. -19.6%; p=0.049). 3. Age was significantly correlated with total BMD (r = 0.66, P = 0.004) trabecular BMD (r = 0.70, P = 0.002)

Evidence Table 4B-2: Observational and Interventional Bone studies using pQCT in CHRONIC stage of SCI (duration >2 yrs)

Author, Year Study Design Setting	Population Characteristics Sample Size Injury Level AIS Score Injury Etiology Mean Age & Range Duration of Injury % Female Baseline Bone Characteristics Osteoporotic Status	Objective or Intervention Comparison Groups	DXA Model & Software (p)QCT Model (p)QCT Scanner Method (p)QCT Imaging Acquisition Measure Sites Timeline of DXA and (p)QCT Scans Outcomes Precision Measures	Relevant Results
Ashe, 2010 Case Series (intervention) Canada	N: 3 Level: C4 – T7; 1 cervical, 2 thoracic AIS: 1 A, 1 B, 1 C Etiology: traumatic Age: mean 33 + 16.4 years Duration: mean 10.8 + 7.3 years % Female: 100 % Ambulatory Status: 3 non-ambulatory, used power or manual wheelchairs Osteoporosis: __	Intervention: Computer controlled leg FES- cycling training 3x/week for 6 months, including habituation and training phases. FES was applied to hamstrings, gluteal, and quadriceps with a pulse duration of 500s at frequency of 60 Hz. Current of the FES was increased from 0 to a preset max with a preset pedaling cadence (max cadence = 32 rpm, fatigue = 18rpm). Phase 1 (Habituation): 2 consecutive sessions of cycling continuously at 35 – 49 rpm for 30 mins. Phase 2 (Training): Resistance increased with an increment of 1/8 kilopod Comparing: BMD before vs. after Complications: Unclear, not monitored.	DXA Model: Hologic 4500; manufacturer standard whole-body analyses. pQCT Model: Stratec XCT 2000; version 5.50 software pQCT Method: 2.5mm slice thickness pQCT Imaging: __ DXA Sites: whole body QCT Sites: 5% and 50% tibia Timeline: Time between DXA-scan and pQCT scan unclear. Follow up after 6 months post intervention. Outcomes: lower-extremity aBMD, pQCT-based BMC (gm/mm) and vBMD LSC: 2%	1. Change in lower extremity aBMD: • Participant 1: ○ Left Leg: 15.63% ○ Right Leg: 7.35% • Participant 2: ○ Left Leg: -1.38% ○ Right Leg: 0.83% • Participant 3: ○ Left Leg: 4.79% ○ Right Leg: 0.2% At the 50% tibia site, vBMD was maintained with 0.51-1.24% change. Change in BMC at 5% tibia site by pQCT: • Participant 1: ○ Left Leg: -5.6% ○ Right Leg: -0.4% • Participant 2: ○ Left Leg: 10.8% ○ Right Leg: 15.1% • Participant 3: ○ Left Leg: 38.1% ○ Right Leg: 2.8% Change in vBMD at 5% tibia site: • Participant 1: ○ Left Leg: -1.6% ○ Right Leg: -1.1% • Participant 2: ○ Left Leg: 12.5% ○ Right Leg: 13.5% • Participant 3: ○ Left Leg: 16.5% ○ Right Leg: -0.5%

Craven, 2017 RCT	FES Group N: 17 (16 completed) Level: C2-T12 AIS: 6 C, 11 D	Intervention: 45 min, 3x/week, 4 months. FES-walking with body weight support group: open-loop FES	Timeline: between March 2005-December 2010; follow-up at 4 months and 12 months; biomarkers followed-up at 4 months	
Canada PEDro=8	Etiology: traumatic Age: mean 56.59 + 14 years Duration: median 5 years, IQR 6.6 % Female: 17.6% Ambulation: __ Mean Change aBMD (g/cm2): Left Total Hip: 0.89 + 0.2 Left Distal Femur: 0.89 ± 0.16 Left Proximal Tibia: 0.71 + 0.18 Mean Change 4% Tbv BMD (mg/cm3): 201.99 + 35.65 Osteoporosis: __ Control Group N: 17 (12 completed) Level: C2-T12 AIS: 7 C, 9 D Etiology: traumatic Age: mean 54.06 + 16.5 years Duration: median 5 years, IQR 18 % Female: 29.4% Ambulation: __ Mean Change aBMD (g/cm2): Left Total Hip: 0.86 + 0.24 Left Distal Femur: 0.81 + 0.18 Left Proximal Tibia: 0.68 + 0.19 Mean Change 4% Tbv vBMD (mg/cm3): 172.91 + 48.10 Osteoporosis: __	(8-125 mA, 0–300 µs pulse duration, 20–50 Hz) over the quadriceps, hamstrings, tibialis anterior and gastrocnemius while walking with body weight support. Control defined as aerobic (20-25 min, 3-5 Borg; arm or leg bicycling or walking in parallel bars. Treadmill if participants were able to walk unassisted) and resistance (2–3 sets of 12–15 repetitions maximum resistance for muscles capable of voluntary contraction) exercise program. Comparing: BMD and biomarkers in intervention group vs. control group Complications: unclear monitoring, not reported Withdrawals Reasons (Total 6): lost to follow-up (3 dropped out, 1 relocated, and 2 medical removal)	Data Source: Clinical examination using DXA, pQCT and blood analysis. DXA Model: 4500A, Hologic Inc, Analyzed by ISCD certified technologist pQCT Model: XCT-2000, Stratec Meziintechnik, Stratec XCT-2000 version 5.50 Outcomes: aBMD (left total hip, right distal femur, and right proximal tibia), vBMD 4% of distal end tibia and 38% of tibial shaft for vBMDcort, vBMDtrab, THlcort, strength-strain index and polar moment of inertia, biomarkers (OC, CTx, Sclerostin)	

Edwards, 2018 RCT North America PEDro=9	TV Population N: 21 (18 completed) Injury Level: 48% cervical, 52% thoracic, 0% lumbar AIS Score: 71% A, 14% B, 10% C, 5% D Injury Etiology: __ Mean Age & Range: mean 46.6 + 15.4 years Duration of injury: 21.1 + 13.4 years % Female: 24% Ambulation: __ Baseline Bone Characteristics: __ Osteoporosis Status: __ TA Population N: 20 (20 completed) Injury Level: 25% cervical, 65% thoracic, 10% lumbar Injury Etiology: __ AIS Score: 70% A, 15% B, 10% C, 5% D Mean Age & Range: mean 47.6 years + 16.3 years Duration of injury: 20.5 + 14.6 years % Female: 15% Baseline Bone Characteristics: __ Osteoporosis Status: All had low bone mass at the total hip or femoral neck (Z-score < -1.5, T-score < -2.5, or T-score < -2.0) and a history of a fragility fracture. VA Population N: 20 (18 completed) Injury Level: 30% cervical, 70% thoracic, 0% lumbar AIS Score: 70% A, 10% B, 20% C, 0% D Injury Etiology: __ Mean Age & Range: mean 40.9 + 16.4 years Duration of injury: 15.4 + 13.4 years % Female: 30% Ambulation: __ Baseline Bone Characteristics: __ Osteoporosis Status: All had low bone mass at the total hip or femoral neck (Z-score < -1.5, T-score < -2.5, or T-score < -2.0) and a history of a fragility fracture	Objective or Intervention: Teriparatide 20 µg/day + vibration 10 min/d (TV), or Teriparatide 20 µg/day + sham vibration 10 min/d (TA), or Placebo + sham vibration 10 min/d (VA). All participants given daily Cholecalciferol 1000 IU as a calcium carbonate and vitamin D supplement. Comparison Groups: baseline vs. follow ups Complications: 11.7% patients had a fragility fracture of the femur or tibia during initial RCT (3 TA, 2 TV, and 2 VA). 8% had a lower extremity fragility fracture during the open-label teriparatide extension study (TA and TV). TV Withdrawal Reasons: nursing home changes (1), lost to follow-up (2) VA Withdrawal Reasons: lost to follow-up (2)	DXA Model & Software: Hologic QDR 4500A (Hologic, Waltham, MA, USA) (p)QCT Model: Sensation 64 Cardiac Scanner (Siemens Medical Systems, Forchheim, Germany) at NU/RIC site and Lightspeed VCT (GE Medical Systems, Milwaukee, WI, USA) at Hines sites (p)QCT Scanner Method: Clinical examination using DXA, CT imaging and blood analysis. (p)QCT Image Acquisition: __ Measure Sites: __ Timeline of DXA and (p)QCT Scans: Jun 2011 – Aug 2015; follow-up after 2 and 6 weeks, and 3, 6, 9 and 12 months. After 12 month RCT, participants were invited to an additional 12 months of open-label Teriparatide and vibration treatment. Outcomes: aBMD (total hip, femoral neck, forearm, whole body), bone resorption biomarkers (CTX, P1NP), bone formation biomarker (BALP), CT analysis of the distal femur and proximal tibia (vBMD of the trabecular bone, and BMC and bone volume of the cortical bone) Precision Measures: __	12 Month Results Relative to Baseline: - TA group had significant changes in: - P1NP (+126%) - CTX (+98.7%) - Bone specific AP (+56.7%) - Femur Metaphyseal cBV (+3.81%), cBMC (+6.71%), and TSI (+3.45%) - Tibia Epiphyseal cBV (+14.3%) and cBMC (+16.2%) - Tibia Metaphyseal cBMC (+3.62%) - Tibia Diaphyseal cBMC (+3.66%) - None of the groups had significant changes in hip, femoral neck, distal femur, and proximal tibia DXA scan results. - TV group had a 1.93% (95%CI [0.65-11.1%]) increase in tibia torsional stiffness. - VA group had an 85.3%, (95%CI [-161--9.58%]) decrease in tibia metaphyseal BMDtot. - While Teriparatide exhibited skeletal activity in chronic SCI patients, no clinical benefit is observed. 24 Month Results Relative to Baseline: - None of the groups had significant changes in hip, femoral neck, distal femur, and proximal tibia aBMD. - Increase in hip aBMD from baseline only observed after 24 months Teriparatide treatment: TA (6.7%, 95%CI [3.4--10.1%]) and TV (4.2%, 95%CI [0.4 - 8.1%]). - P1NP and BSAP levels increased significantly in TA (102%; 11.5%), TV (58.0%; 10.9%), and VA (104%; 12.6%) groups. - A significant increase in diaphyseal cBMC was observed in all three groups (TA: 3.36%; TV: 3.73%; VA 4.39%). - Both TV and VA groups experienced significant increases in tibia metaphyseal cBV, cBMC, CSI, and TSI (TV: 5.11%, 7.64%, 14.0%, 6.95%; VA: 2.96%, 6.28%, 11.9%, 6.42%), femur epiphyseal cBV and cBMC (TV: 17.9%, 19.4%; VA: 21.7%, 23.4%), and femur metaphyseal TSI (TV: 8.86%; VA: 6.67%) A significant change in femur diaphyseal cBMC was only observed in TV group (20.0%)
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El-Kotob, 2017 (Conference abstract only) Longitudinal USA	Chronic SCI N: 70 Injury Level: C2-T12; tetraplegia (51%), motor complete injuries (64%) AIS Score: AIS A-D Injury Etiology: __ Mean Age (SD): 48.8 (11.5) years Duration of Injury (SD): 15.5 (10.0) years % Female: 29% Baseline Bone Characteristics: TrabvBMD: 140.1 (53.0) Osteoporotic Status: __	Objective or Intervention: To determine whether trabecular volumetric bone mineral density (TrabvBMD) continues to decline Comparison: __	DXA Model & Software: __ (p)QCT Model: __ (p)QCT Scanner Method: __ (p)QCT Imaging Acquisition: software (Stratec), the CALCBD mode was applied with contour mode 3, peel mode 2, outer threshold of 130 mg/cm³, and inner threshold of 400 mg/cm³. Measure Sites: 4% tibia Timeline of DXA and (p)QCT Scans: baseline, year 1, and year 2 Outcomes: TrabvBMD Precision Measures: Repeated measures analyses of variance were performed to examine whether TrabvBMD (mg/cm³) changes between the study time points in the total sample and in subgroups of participants	TrabvBMD was not significantly different between baseline, year 1 [143.3 (55.8)] and year 2 [134.0 (51.2)]: • $V=0.077$, $F(2,40)=1.674$, $p=0.200$. No statistically significant mean group changes over two years: • In the total sample [$V=0.078$, $F(2,38)=1.618$, $p=0.212$] • In subgroups of participants with complete ($p=0.277$) and incomplete injuries ($p=0.627$). TrabvBMD changes ranged from: • -183.6 to 207.6 mg/cm³ at year 1 • -188.2 to 76.4 mg/cm³ at year 2 At year 2, the mean TrabvBMD difference was -6.1 mg/cm³ [95% CI (-18.0, 5.9)] • compared to the least significant change (LSC) for TrabvBMD of ± 10.45 mg/cm³, an increase was observed in 5 participants (DOI:3-28 years) and a decrease in 7 individuals (DOI:2-14 years) No significant differences between the study time points (TrabvBMD is maintained at the distal tibia, even after controlling for DOI) Some inter-individual variability in BMD over time.
Frotzler, 2008 Longitudinal Switzerland	SCI N: 89 (39 completed) Injury Level: __ IS Score: __ Injury Etiology: traumatic Age: mean 42.0 + 13.4 years Duration of Injury: 12.0 + 10.8 years % Female: 0% BMD: 4% Tibia: BMC = 1.82 (0.27) BMDtot = 134.97 (23.93) BMDtrab = 70.09 (22.70) 4% Femur: BMC = 5.77 (0.86) BMDtot = 144.48 (24.26) BMDtrab = 116.02 (24.13) Osteoporotic Status: __	Objective or Intervention: aim of the present study was to verify the presence of our previously suggested bone steady-state based on cross-sectional data in a longitudinal study design. Furthermore, since time post injury was documented to be negatively related to bone loss after SCI, we aimed to test this relation in subjects with chronic SCI after the initial bone loss is complete Comparison Groups: __ Complications: __	(p)QCT Imaging Acquisition: Image processing were performed using manufacturers software package Measure Sites: 4% Tibia 38% Tibia 4% Femur 25% Femur Timeline of DXA and (p)QCT Scans: pQCT at 0, 15, 30 months DXA – none	4% Tibia - t15 (months) • BMC - 1.81 (0.27) • BMDtot - 134.49 (23.54) • BMDtrab - 69.77 (23.08) 4% Tibia - t30 (months) • BMC - 1.71 (0.27) • BMDtot - 134.25 (24.04) 4% Femur - t15 (months) • BMC - 5.77 (0.91) • BMDtot - 144.02 (24.00) • BMDtrab - 115.80 (25.39) 4% Femur - t30 (months) • BMC - 5.76 (0.88) • BMDtot - 143.43 (21.24) • BMDtrab - 114.51 - (22.41) • BMDtrab - 68.92 (22.96)

			Outcomes: Bone measurements were performed in each individual three times within a time period of 30 months: at baseline (t0), at 15 months (t15) and at 30 months (t30). Precision Measures: In order to test whether changes in an individual's bone parameters between t0, t15 and t30 were a real change at the 95% confidence level, the minimal detectable change (MDC95%) was calculated	
Frotzler, 2008 Pre-Post (intervention) Switzerland/UK	N: 12 (11 Completed) Level: 1 T3, 4 T4, 1 T5, 1 T6, 2 T7, 2 T9; complete AIS: 11 A Etiology: traumatic Age: mean 41.9 ± 7.5 years Duration: mean 11.0 ± 7.1 years % Female: 18.2% Ambulation: ___ Baseline bone characteristics: Mean BMC (g/cm): 4% femur: 6.21 ± 1.30; 4% tibia: 2.14 ± 0.84 38% tibia: 3.51 ± 0.73 4% proximal tibia: 3.59 ± 0.91 Mean vBMDtot (mg/cm3): 4% femur: 157.90 ± 24.17 4% tibia: 166.37 ± 56.98 38% tibia: ___ 4% proximal tibia: 124.44 ± 27.98 Mean CSAtot (mm2): 4% femur: 3924.94 ± 537.72 4% tibia: 1281.65 ± 177.91 38% tibia: 454.01 ± 73.88 4% proximal tibia: 2905.32 ± 546.00 Mean vBMDtrab (mg/cm3): 4% femur: 122.10 ± 25.21 4% tibia: 100.52 ± 57.28 38% tibia: ___ 4% proximal tibia: 71.62 ± 25.34 Osteoporosis: ___	Intervention: 3 phase intervention Phase 1: Isometric bilateral FES (30-60 mins, 3-5x/week); pulse frequency of 50 Hz, width of 300–400 µs, amplitude 80-150 mA, 1:1 duty cycle set at 6 s on/off; electrodes placed proximally and distally to motor points of gluteus, quadriceps, and hamstring. Phase 2: FES-cycle training (10-60 mins, 3-4x/week, 3 months); pulse frequency of 50 Hz, width of ≤500 µs, amplitude adjusted to participant needs; electrodes placed bilaterally on gluteus, quadriceps, hamstrings, as well as triceps surae in 5 participants. Phase 3: High volume FES-cycling (60 mins, 5x/week, 9 months) Comparing: pre vs. post intervention Complications: monitored, none-reported Withdrawals Reasons (Total 1): Foot fracture occurred at 7 months, unrelated to intervention.	Timeline: measurements at baseline, 6 months, and 12 months. Data Source: clinical examinations using pQCT pQCT Model: XCT 3000, Stratec Medical; manufacturer's software, version 5.50 E Outcomes: BMC (4% femur; 4%, 38% tibia; 4% proximal tibia), CSAtot (4% femur; 4%, 38% tibia; 4% proximal tibia), BMDtot (4% femur; 4% tibia; 4% proximal tibia), BMDtrab (4% femur; 4% tibia; 4% proximal tibia), CSAcort (38% tibia), THlcort (38% tibia), BMDcort (38% tibia)	Significant results between baseline and 6 months: • None-reported Significant results between baseline and 12 months: • 4% femur: ○ BMDtrab increased 14.4 ± 21.1%, p=0.05 ○ BMDtot increased 7.0 ± 10.8%, p=0.05 Significant results between 6 months and 12 months: • 4% femur: ○ BMDtrab increased by 3.1 ± 3.2%, p=0.016 ○ BMDtot increased 1.3 ± 1.7%, p=0.041 ○ CSAtot increased 1.2 ± 1.5%, p=0.001 All results: • 6 month follow-up mean values: ○ 4% femur: ✦ BMC: 6.46 ± 1.19 g/cm ✦ BMDtot: 166.22 ± 25.14 mg/cm3 ✦ CSAtot: 3908.87 ± 560.15 mm2 ✦ BMDtrab: 133.49 ± 23.33 mg/cm3 ○ 4% tibia: ✦ BMC: 2.13 ± 0.82 g/cm ✦ BMDtot: 165.24 ± 55.82 mg/cm3 ✦ CSAtot: 1283.74 ± 185.51 mm2 ✦ iBMDtrab: 99.71 ± 55.64 mg/cm3 ○ 38% tibia: ✦ BMC: 3.52 ± 0.69 g/cm ✦ CSAtot: 455.53 ± 74.44 mm2 ✦ 4% proximal tibia: ✦ BMC: 3.55 ± 0.86 g/cm ✦ BMDtot: 123.62 ± 27.46 mg/cm3 ✦ CSAtot: 2906.75 ± 592.27 mm2 ✦ iBMDtrab: 69.65 ± 23.00 mg/cm3 • 12 month follow-up mean values:

				○ 4% femur: ✦ BMC: 6.64 ± 1.30 g/cm ✦ BMDtot: 168.41 ± 26.51 mg/cm³ ✦ CSAtot: 3958.31 ± 571.72 mm² ✦ iBMDtrab: 137.41 ± 25.26 mg/cm³ ○ 4% tibia: ✦ BMC: 2.14 ± 0.84 g/cm ✦ BMDtot: 166.91 ± 56.85 mg/cm³ ✦ CSAtot: 1279.68 ± 180.07 mm² ✦ iBMDtrab: 100.73 ± 57.28 mg/cm³ ○ 38% tibia: ✦ BMC: 3.51 ± 0.69 g/cm ✦ CSAtot: 454.45 ± 73.71 mm² ○ 4% proximal tibia: ✦ BMC: 3.52 ± 0.88 g/cm ✦ BMDtot: 122.50 ± 26.82 mg/cm³ ✦ iCSAot: 2900.27 ± 571.32 mm² ✦ iBMDtrab: 69.17 ± 23.02 mg/cm³
Frotzler, 2009 Pre-Post (detraining) Switzerland / UK	N: 5 Level: T4-T7, paraplegic; complete AIS: 5 A Etiology: traumatic Age: mean 38.6 ± 8.1, range 27.7-48.4 years Duration: mean 11.4 ± 7.0 years % Female: 20 % Ambulation: __ BMD: __ Osteoporosis: __ Baseline values were published in their previous study (Frotzler et al., 2008).	Intervention: Follow-up on Frotzler et al., 2008, with intention to show the effect of detraining post FES-cycling intervention. 4 participants stopped FES-cycling and 1 reduced training to 30 mins, 2- 3x /week, from 60 mins, 5x / week) Comparing: pre- high volume training vs. post detraining/reduced training Complications: Unclear, not monitored.	Timeline: measurements at baseline pre-intervention, post-high volume training, 6 and 12 months post high volume training. Data Source: Clinical examination using pQCT. pQCT Model: XCT 3000, Stratec Medical; manufacturer's software, version 6.0 B Outcomes: 4% femur (BMC, BMDtot, and BMDtrab), 4% tibia (BMC, BMDtot, and BMDtrab)	Participants that stopped FES-cycling intervention (n=4) 4% femur (% of bone parameter gained in first 6 months of training that was preserved after 12 months of detraining): BMDtrab: $73 \pm 13.4\%$ 4% femur (% of bone parameter gained in first 6 months of training that was preserved after 12 months of detraining): BMDtot: $63.8 \pm 8.0\%$ BMC: $59.4\% \pm 3.9\%$ Tibia: Bone parameters changed between -1.3-1.6%. Participant with reduced FES-cycling intervention (n=1): 4% distal femur % of bone parameter gain from training that was preserved after 12 months of detraining): BMDtot: 96.2% BMDtrab: 95% Tibia: Bone parameters decreased by 1.3-4.8%
Giangregorio, 2006 Pre-post (intervention) Canada	SCI N: 14 (13 complete) Injury Level: C4-T12; 11 cervical, 3 thoracic; incomplete AIS Score: 2 B, 12 C Injury Etiology: traumatic Age: mean 27.2, 20-53 years Duration of Injury: mean 7.4, 1.2-24 years % % Female: 15.4% Baseline Bone Characteristics: Mean 66% tibia	Objective or Intervention: Body-weight-supported treadmill training (BWSTT), 12 – 15 months. Completed protocol 3x/week for 144 sessions; intensity and duration increased as tolerated Comparing: before vs. after Complications: 1 pressure sore, 1 occasional knee pain	DXA Mode &Software: Hologic 4500A densitometer, Bedford, Mass (p)QCT Model: General Electric (GE) CTI Scanner (GE, Milwaukee, Wis.) (p)QCT Scanner Method: Clinical examination using DXA, CT and urinary analysis. (p)QCT Imaging Acquisition: __	BWSTT Group: 1. No significant changes in bone geometry or vBMD after intervention: a. 66% tibia ✦ vBMD: 727.8 ± 71.4 g/cm³ ✦ BMC: 1384.2 ± 251.1 g ✦ CSAcort: 291.0 ± 60.2 mm² ✦ vBMDcort: 834.2 ± 38.0 g/cm³ b. 60% femur ✦ vBMD: Mean 758.1 ± 85.2 g/cm³ ✦ BMC: 1626 ± 363.8 g

Giangregorio, 2006 Pre-post (intervention) Canada	vBMD: 745.0 ± 87.8 g/cm³ BMC: 1437.3 ± 281.9 g Cortical vBMD: 851.3 ± 56.4 g/cm³ Cortical CSA: 297.0 ± 67.5 Mean Mid-femur : vBMD: 770.4 ± 89.0 g/cm³ BMC: 1673.9 ± 394.7 Control defined as no intervention. N: 4 (3 complete) Injury Level: C5-T12; 3 cervical, 1 thoracic; AIS Score: 2B, 2D Injury Etiology: traumatic Mean Age & Range: mean 38, range 32-41 years Duration of Injury: mean 14.8, range 3-25 years % Female: 0% Baseline Bone Characteristics: __ Osteoporotic Status: __	Comparison Groups: __ Complications: Withdrawal reasons (Control): 1 personal reasons Withdrawal Reasons (Intervention): 1 noncompliance	Measure Sites: __ Timeline of DXA and (p)QCT Scans: follow-up after 144 sessions (12-15 months); urinary analysis after 72 sessions Outcomes: DXA derived aBMD (hip, distal femur and proximal tibia), CT derived vBMD (60% femur site and 66% tibia site) and bone CSA, bone formation biomarkers (OC) and bone resorption biomarkers (DPD). Precision Measures: __	✦ CSAcort: 353.0 ± 89.8 mm² ✦ vBMDcort: 840.9 ± 43.4 g/cm³ - OC remained at the high end of normal ranges of 3.7–10.0 ng/ml for females and 3.4–9.1 ng/ml for males. - DPD levels were elevated at baseline with 13.8 ± 18.1 nmol DPD/mmol Cr and remain elevated with 12.5 ± 15.3 nmol DPD/mmol Whole Body: - BMD: Mean 1.118 ± 0.1 g/cm² - Osteoporosis: - Femoral: 8 osteoporosis, 3 osteopenic, 2 normal Cr after 144 sessions. No significant difference between baseline, 72 and 144 sessions. - Whole-body BMD decreased to 1.094 ± 0.1 g/cm² (p=0.006). Control Group: Only 1 participant had a reduction in proximal femur BMD, 2 had reductions in the proximal tibia BMD, and all 3 had reductions in distal femur BMD by 0.9–8.6%.
Lambach, 2018 Pre-post (intervention) California, USA	N: 4 Injury Level: C7- T10; 1 cervical, 3 thoracic AIS Score: 2 A, 2 B Etiology: traumatic Age: mean 32.5 ± 8.5 years Duration of Injury: mean 12.5 ± 2.65 months % Female: 0% Ambulation: __ Baseline Bone Characteristic: __ Osteoporotic Status: __	Intervention: 90 FES sessions over 9–12 months, each session lasting from 30–60 mins with up to 30 min of active training time. Muscle Conditioning: Seated FES leg extension/ flexion exercises were used. Stimulation was applied to one quadriceps and the hamstrings of the contralateral limb. Stimulation pulses were 450 μs delivered at 40 Hz, with an intensity of 0–120 mA. Stimulation lasted 5 s followed by 1 s of rest. Same protocol was applied to the opposite limb. Once the participant was capable of 30 min of FES muscle conditioning, maintaining and full knee extension then they progressed to FES rowing. FES Rowing: Stimulation was applied bilaterally to the quadriceps and hamstrings. Movement involved leg extension	DXA Model & Software: __ (p)QCT Model: XCT3000, Stratec; XCT 6.00B software (p)QCT Scanner Method: __ (p)QCT Imaging Acquisition: __ Timeline of DXA and (p)QCT Scans: Follow ups at baseline, after 30, 60 and 90 exercise sessions Outcomes: Trabecular vBMD (4% femur and 4% tibia) BMC, and total vBMD Precision Measures: __ Comparing: before vs. after Complications: initial mild autonomic dysreflexia (3 participants) and shoulder discomfort (3 participants) Data Source: Clinical examinations using the pQCT	Trabecular vBMD of Distal Femur Results: - Bone stimulus correlated with change in vBMD (p=0.017; R²=0.452). - Average number of weekly training sessions attended correlated with change in vBMD (p<0.001; R²=0.700) Baseline vs. Session 30 - All participants declined (Range: -5% to -11% of baseline). Session 30 vs. Session 60 2 participants had a reduced rate of vBMD loss from -7% to -3% and from -5% to 0%. 2 participants had a 6% and 8% increase in trabecular vBMD. Session 30 vs. Session 60 3 participants experienced little or no vBMD loss in the distal femur (Range: -1% to +2%). 1 participant had a return of bone loss of -10%. Trabecular vBMD of tibia Results: - Similar trend as femur trabecular BMD loss. BMC and total BMD results were not reported.

		first followed by flexion of the arms when the legs reached mid- to near-extension. Participants started off with short intervals (1 – 3 mins) then they progressed to 30 continuous minutes. Comparison Groups: __		
Morse, 2019 RCT USA PEDro=6	Zoledronate + Functional Electrical Stimulation (FES) Rowing Group N: 20 (10 analyzed) Level: 8 motor complete AIS Score: __ Injury Etiology: __ Mean Age: mean 38.3 + 13.6 years Duration of Injury: mean 8.8 + 11.1 years % Female: 10% Baseline Bone Characteristics: Total Hip: 0.77 + 0.17 Femoral Neck: 0.82 + 0.18 Distal Femur: 0.76 + 0.21 Proximal Tibia: 0.76 + 0.25 Osteoporotic Status: 3 normal aBMD, 4 osteopenia, 3 osteoporosis FES Rowing Group N: 18 (10 analyzed) Injury Level: 7 motor complete AIS Score: __ Injury Etiology: 7 motor complete Mean Age: mean 38.2 + 11.8 years Duration of Injury: mean 14.4 + 14.1 years % Female: 10% Baseline Bone Characteristics: Total Hip: 0.82 + 0.29 Femoral Neck: 0.85 + 0.30 Distal Femur: 0.83 + 0.36 Proximal Tibia: 0.82 + 0.34 Osteoporotic Status: 3 normal BMD, 4 osteopenia, 3 osteoporosis	Intervention: 12- month FES-rowing-exercise program with or without a 1-time dose of Zoledronate (15 minute infusion of 5 m/100mg solution). Comparing: before vs. after; Zoledronate + FES rowing group vs. FES rowing group; duration of injury	DXA Model: GE Healthcare iDXA 5 Gen.; enCore configuration V12.3 software QCT Scanner 1 Model: Definition Flash Method: 120 kVp; 170 – 200 mAs; asynchronous calibration Imaging: 0.3 – 0.5 mm pixel resolution; slice 0.5mm thickness; 0.15 g/cm³ threshold for periosteal surface boundary, cortical bone were regions with bone-equivalent density >0.33 g/cm³ QCT Scanner 2: Model: LightSpeed Pro 16 Method: 120 kVp; 50 mA; asynchronous calibration Imaging: 0.652 - 0.977 mm pixel resolution; 0.625 - 1.250 mm slice thickness; 0.15g/cm³ threshold for periosteal surface boundary, cortical bone were regions with bone-3 equivalent density > 0.33g/cm DXA Sites: distal femur, proximal tibia, femoral neck and total hip QCT Sites: epiphysis (0 - 10% segment length), and metaphysis (10 - 20% segment length) of the distal femur and proximal tibial metaphyses Timeline: Time between DXA-scan and pQCT scan unclear. Follow up after 12 months. Outcomes: aBMD, QCT-based BMC, BV, bending strength index, compressive strength (CSI), cortical thickness (THIcort) index, and buckling ratio	Compared to the FES Rowing Group, Zoledronate + FES Rowing group had greater: 1. Cortical BV at the proximal tibial metaphysis by 345 + 109 mm³ (p=0.006) and the distal femoral metaphysis by 471 + 225 mm³ (p=0.05). 2. Cortical thickness index by 0.012 + 0.004 mm at the proximal tibia (p=0.013) and by 0.016 + 0.006 mm at the distal femur (p=0.009) 3. Buckling ratio by 4.51 + 1.73 at the proximal tibia (p=0.019) and by 5.47 + 2.04 at the distal femur (p=0.015) FES Rowing Results: 1. Gains in THIcort index and buckling ratio at the tibial metaphysis were dose- dependent on total amount of exercise performed (p=0.04 to 0.007). 2. For buckling ratio, ~2.533 kWh of FES rowing work was equivalent to the benefits of a 1-time Zoledronate infusion.

			DXA Precision Measures: At the distal femur, the RMS-CV for aBMD was 2.3% and the corresponding RMS-SD was 0.012 g/cm². At the proximal tibia, the RMSCV for aBMD was 2.4%, and the corresponding RMS-SD was 0.028 g/cm². QCT Precision Measures: For the 3D-registration algorithm the RMS-CV for BMC was 0.96%, vBMD was 0.91%, and BV was 0.60%.	
Wuermsr, 2015 Pre-post (intervention) USA	N: 12 (9 completed) Injury Level: paraplegic; complete AIS Score: A or B Injury Etiology: _ Mean Age & Range: mean 42 + 8 years Duration of Injury: 2-27 years % % Female: 44.4% Ambulation: unable to stand without bracing or standing frame. Baseline Bone Characteristics: Total hip: 0.71 ± 0.22 Femur neck: 0.75 ± 0.20 Mean vBMD (mg/cm³) Tibia total: 167.69 ± 64.73 Tibia trabecular: 67.53 ± 54.58 Tibia cortical: 809.84 ± 52.87 Osteoporotic Status: _	Objective or Intervention: Whole-body low-magnitude vibration (Juvent 1000) using a standing frame for 20 min/day, 5 days/week, and for 6 months. The vibrating plate provided a 0.3 g, 34 Hz vertical sinusoidal movement of ~50µm. Comparison Groups: before vs. during vs. after Complications: neuropathic pain (1 participant), increase spasticity while standing, revision surgery for spinal implants (1 participant); relationship between complications and intervention not clarified Complications: Withdrawal Reasons: Inability to commit time (3 participants) States no control group, but control-like data included. Unclear if same participants across follow-ups, so characteristics were not extracted.	DXA Model & Software: Lunar Prodigy system (GE Healthcare, Madison, WI, USA) pQCT Model: XtremeCT, Scanco Medical AG, Brüttisellen, Switzerland (p)QCT Scanner Method: _ (p)QCT Imaging Acquisition: _ Timeline: follow-up at 3, 6 and 12 months Data Source: Clinical examination using DXA, high-resolution pQCT, self-reported use of intervention, and blood analysis. Outcomes: total hip and femur neck aBMD, tibia vBMDcort, tibia vBMDtrab, tibia vBMDtot and bone reabsorption biomarkers (CTX, P1NP and serum sclerostin) Precision Measures: _	1. Femoral neck aBMD; 0.3% tibia vBMD tot, 0.4% tibia vBMDtrab, 0.4% tibia vBMDcort 2. CV: 0.9% total hip, 2.7% 3. Three participants had an increase in total hip aBMD greater than the minimal detectable change (not defined). 4. Overall, no significant differences at 6- or 12-month follow-ups for all outcomes: a. Mean total hip aBMD (g/cm²): ✦ 6 month: 0.69 ± 0.21 ✦ 12 month: 0.70 ± 0.20 b. Mean femur neck aBMD (g/cm²): ✦ 6 month: 0.74 ± 0.18 ✦ 12 month: 0.75 ± 0.16 c. Mean tibia vBMDtot (mg/cm³): ✦ 6 month: 163.25 ± 64.18 ✦ 12 month: 159.98 ± 59.32 d. Mean tibia vBMDtrab (mg/cm³): ✦ 6 month: 64.66 ± 52.68 ✦ 12 month: 63.99 ± 49.95 e. Mean tibia vBMDcort (mg/cm³): ✦ 6 month: 804.23 ± 66.80 ✦ 12 month: 793.51 ± 62.48 f. Mean CTX (ng/ml): ✦ Baseline: 0.25 ± 0.15 ✦ 6 month: 0.26 ± 0.12 ✦ 12 month: 0.23 ± 0.17 g. Mean P1NP (µg/l): ✦ Baseline: 52.86 ± 24.05 ✦ 6 month: 48.38 ± 20.53 ✦ 12 month: 54.95 ± 23.00 h. Mean sclerostin (pmol/l): ✦ Baseline: 27.04 ± 13.24 ✦ 6 month: 29.43 ± 10.88 ✦ 12 month: 31.98 ± 16.98

Evidence Table 4C: (p)QCT Precision for Measuring Lower Extremity Bone Health

Author, Year Study Design Setting	Population Characteristics Sample Size Injury Level AIS Score Injury Etiology Mean Age & Range Duration of Injury % Female Baseline Bone Characteristics Osteoporotic Status	Objective or Intervention Comparison Groups	DXA Model & Software (p)QCT Model (p)QCT Scanner Method (p)QCT Imaging Acquisition Measure Sites Timeline of DXA and (p)QCT Scans Outcomes Precision Measures	Precision Relevant Results
Edwards, 2013 Longitudinal Study USA	N: 13 Level: C4-T11; 9 cervical, 4 thoracic AIS: 4 A, 8 B, 1 C Etiology: __ Age: mean 25.9, 19 - 64 years Duration: mean 2.1, 1.0 – 3.8 months % Female: 30.8% Bone Characteristics: Femoral Neck (Mean, SD) vBMDtot: 0.386 + 0.051 g/cm ³ vBMDtrab: 0.242 + 0.060 g/cm ³ Cortical BMC: 7.50 + 2.14 g Osteoporosis: __	Objective: Quantify changes to bone mineral, geometry, and measures of strength at the proximal femur in acute SCI Comparing: scan precision from 6 SCI participants	Model: Sensation 64 C Method: 120 kVp, 280 mA, image alignment using Mimics software Imaging: pixel resolution 0.352 mm, slice thickness 1 mm; synchronous calibration Sites: right femoral neck Timeline: 2 scans separated by Mean 3.5 months, Range 2.6 – 4.8 months Precision Outcomes: RMS-SD, RMS-CV% of vBMD, BMC and geometry Bone Outcomes: vBMD (total, trabecular, cortical), and cortical BMC	1. RMS SD (Pooled Baseline & Follow-up): a. vBMDtot: 0.002 g/cm ³ b. vBMDtrab: 0.003 g/cm ³ c. Cortical BMC: 0.271 g 2. RMS CV% (Pooled Baseline & Follow-up): a. vBMDtot: 0.6% b. vBMDtrab: 1.0% c. Cortical BMC: 1.5%
Eser, 2004 Cross-sectional Switzerland	SCI N: 89 Level: 65 paraplegic, 24 tetraplegic; 80 spastic lesion (lesion level C5–T12) and 9 flaccid lesion (lesion level L1–L3) AIS: __ Etiology: all traumatic Age: mean 41.5 + 14.2 years Duration: mean 12.0 + 11.3 years Bone characteristics: 4% Femur (Mean, SD) CSAtot: 4010 + 365 mm ² vBMDtot: 146.5 + 29.1 mg/cm ³ vBMDtrab: 112.8 + 28.3 mg/cm ³ 4% Tibia (Mean, SD)	Objective: Describe bone loss of trabecular and cortical bone, and bone geometry of a SCI individuals. Comparing: scan precision from 7 SCI participants	Model: Stratec XCT 3000 Epiphyseal Method: 180mg/cm ³ threshold for periosteal surface of the tibia and 150mg/cm ³ threshold for the femur; vBMDtrab using 45% peel method; asynchronous calibration Diaphyseal Method: 280mg/cm ³ threshold for periosteal surface; 710mg/cm ³ threshold for cortical bone; asynchronous calibration Imaging: 0.5mm voxel size at tibia, 0.3mm voxel size at femur; 2mm slice thickness	Results: 1. 4% Femur RMS SD and CV%: a. CSAtot: 50.4 mm ² , 1.25% b. vBMDtot: 3.31 mg/cm ³ , 2.04% c. vBMDtrab: 2.25 mg/cm ³ , 1.80% 2. 4% Tibia RMS SD and CV%: a. CSAtot: 16.1 mm ² , 1.23% b. vBMDtot: 0.67 mg/cm ³ , 0.46% c. vBMDtrab: 1.49 mg/cm ³ , 2.23% 3. 38% Tibia RMS SD and CV%: a. CSAtot: 1.22 mm ² , 0.26% b. CSAcort: 1.09 mm ² , 0.42% c. vBMDcort: 3.42 mg/cm ³ , 0.30%

	CSAtot: 1324 + 192 mm² vBMDtot: 135.0 + 26.9 mg/cm³ vBMDtrab: 66.1 + 23.4 mg/cm³ 38% Tibia (Mean, SD) CSAcort: 249.3 + 59.3 mm² CSAtot: 464.8 + 66.1 mm² vBMDcort: 1125.9 + 52.6 mg/cm³ Osteoporosis: __		Epiphyseal Sites: 4% of femur and tibia Diaphyseal Sites: 38% of tibia Timeline: 2 measures of femur and tibia for precision analysis Precision Outcomes: RMS-SD and RMS-CV% Bone Outcomes: vBMDtot, vBMDtrab, CSA, and, vBMDcort,	
Giangregorio, 2013 Cross-sectional Canada	SCI N: 14 (12 analyzed) Level: C5 – L1 AIS: __ Etiology: all traumatic (5 motor vehicle accident, 3 diving, 1 fall, 1 gunshot wound 1, and 1 football) Age: mean 43.8 + 9.3 years Duration: mean 19.9 + 13.3 years % Female: 25% Male SCI Bone Characteristics Tibia 4% (Mean, SD) vBMDtrab: 109.3 + 40.2 mg/cm³ vBMDtot: 149.8 + 59.3 mg/cm³ CSAtot: 1314.9 + 198.9 mm² Tibia 66% (Mean, SD) CSAcort: 253.1 + 58.4 mm² Female SCI Bone Characteristics Tibia 4% (Mean, SD) vBMDtrab: 126.6 + 40.4 mg/cm³ vBMDtot: 159.9 + 19.6 mg/cm³ CSAtot: 1108.2 + 116.6 mm² Tibia 66% (Mean, SD) CSAcort: 221.3 + 34.0 mm² Osteoporosis: __	Objective: Precision of pQCT imaging of SCI participants compared to participants without SCI. Comparing: scan precision; SCI vs. non-SCI participants	Model: Stratec XCT-2000 Ultra-distal Tibia Method: trabecular bone defined with contour mode 3, peel mode 2 and a 130/400 mg/cm³ threshold in CALCBD mode was; Stratec XCT V6.0 software Tibia Shaft Method: Cortical bone defined with contour mode 1 and a 710 mg/cm³ threshold in CORTBD mode; Osteo-Q and Stratec XCT V6.0 software Imaging: 0.2 voxel size for ultra-distal tibia; 0.5 voxel size for tibia shaft; 2.5mm slice thickness Sites: tibia epiphysis (4%) and shaft (66%) Timeline: repeated scan on the same day Precision Outcomes: RMS-SD, RMS-CV% and LSC of vBMD and geometry variables Bone Outcomes: vBMD, and CSA	1. RMS-SD Results for SCI vs. Non-SCI: Tibia 4% a. vBMDtrab: 1.64 vs. 4.56 mg/cm³ b. vBMDtot: 1.38 vs. 7.19 mg/cm³ c. CSAtot: 34.81 vs. 44.05 mm² Tibia 66% d. CSAcort: 1.73 vs. 2.25 mm² 2. RMS-CV% Results for SCI vs. Non-SCI: Tibia 4% a. vBMDtrab: 2.3 vs. 1.87% b. vBMDtot: 0.95 vs. 2.27% c. CSAtot: 2.70 vs. 4.27% Tibia 66% d. CSAcort: 0.86 vs. 0.68% 3. LSC Results for Pooled from SCI & Non-SCI (RMS-SD, RMS-CV%): Tibia 4% a. vBMDtrab: 10.45 mg/cm³, 5.6% b. vBMDtot: 16.06 mg/cm³, 5.3% c. CSAtot: 113.4 mm², 10.5% Tibia 66% d. CSAcort: 5.69 mm², 2.1%
Gibbs, 2018 Cross-sectional Canada	SCI N: 19 Level: __ AIS: 19 A-C Etiology: __ Age: mean 43.5 ± 8.6 years % Female: 21.1% Bone characteristics: 66% Tibia (Mean, SD): vBMDcort: mean 1098.8 ± 36.7 mg/cm³	Objective: Compare test-retest precision error for pQCT-derived marrow density and marrow area segmentation at the tibia using 3 software packages. Comparing: SCI group vs. control groups; Stratec-TB method vs. BoneJ-TB method vs. Sliceo-WS method	Model: Stratec XCT- 2000 vBMDcort Method: CORTBD analysis with a threshold of 710 mg/cm³ and contour mode 1 Marrow Identification Stratec-TB Method: used CALCBD analysis with an 280mg/cm³ outer density threshold and an 100mg/cm³ inner density threshold	1. RMS-SD for SCI vs. Young Adults vs. Older Adults: Marrow Density (mg/cm³) a. Stratec-TB: 2.46 vs. 2.61 vs. 3.59 b. BoneJ-TB: 2.78 vs. 2.69 vs. 3.45 c. Sliceo-WS: 2.12 vs. 2.62 vs. 3.30 Marrow Area (mg/mm²) a. Stratec-TB: 3.57 vs. 3.20 vs. 6.99 b. BoneJ-TB: 3.81 vs. 3.98 vs. 6.99

	Mean Marrow Density (mg/cm³) Stratec-TB: 23.1 ± 8.3 BoneJ-TB: 22.2 ± 7.7 Sliceo-WS: 23.0 ± 9.1 Mean Marrow Area (mm²) Stratec-TB: 210.6 ± 91.7 BoneJ-TB: 161.4 ± 71.4 Sliceo-WS: 203.9 ± 92.7 Osteoporosis: __ Controls Young Adults N: 18 Age: mean 25.4 ± 3.2 years % Female: 61.1% Bone characteristics: 66% Tibia (Mean, SD): vBMDcort: 1134.1 ± 31.6 mg/cm³ Mean Marrow Density (mg/cm³) Stratec-TB: 23.5 ± 7.6 BoneJ-TB: 23.3 ± 7.6 Sliceo-WS: 22.9 ± 8.0 Mean Marrow Area (mm²) Stratec-TB: 159.3 ± 49.2 BoneJ-TB: 144.0 ± 46.6 Sliceo-WS: 153.7 ± 46.6 Osteoporosis: __ Controls Older Adults N: 47 Age: Mean 71.8 ± 8.2 % Female: 100% Bone characteristics: 66% Tibia (Mean, SD): vBMDcort: 1069.7 ± 42.5 mg/cm³ Mean Marrow Density (mg/cm³) Stratec-TB: 21.2 ± 8.7 BoneJ-TB: 20.6 ± 8.5 Sliceo-WS: 20.7 ± 8.4 Mean Marrow Area (mm²) Stratec-TB: 164.8 ± 48.6 BoneJ-TB: 149.4 ± 46.5 Sliceo-WS: 161.9 ± 48.0 Osteoporosis: __		BoneJ-TB Method: used ImageJ version 1.48 and BoneJ macros Sliceo-WS Method: guided by the watershed algorithm using Morpho mode from SliceOmatic software, version 4.3 Imaging: 500 um in-plane resolution; 15mm/s scanner speed, 2.0 ± 0.5mm slice thickness Sites: 66% tibia Timeline: repeated scan on same day Precision Outcomes: LSC, RMS-SD, RMS-CV%, and ICC Bone Outcomes: vBMDcort, marrow density, and marrow area	d. Sliceo-WS: 4.56 vs. 3.79 vs. 6.94 2. RMS-CV% for SCI vs. Young Adults vs. Older Adults: Marrow Density (%) a. Stratec-TB: 12.23 vs. 12.84 vs. 28.50 b. BoneJ-TB: 15.63 vs. 14.46 vs. 25.22 c. Sliceo-WS: 10.86 vs. 13.94 vs. 23.02 Marrow Area (mg/mm²) d. Stratec-TB: 1.88 vs. 1.93 vs. 4.36 e. BoneJ-TB: 2.58 vs. 2.60 vs. 5.10 f. Sliceo-WS: 2.35 vs. 2.42 vs. 4.56 3. LSC Results for SCI vs. Young Adults vs. Older Adults: Marrow Density (mg/cm³) a. Stratec-TB: 6.81 vs. 7.22 vs. 9.95 b. BoneJ-TB: 7.70 vs. 7.45 vs. 9.57 c. Sliceo-WS: 5.87 vs. 7.25 vs. 9.14 Marrow Area (mm²) a. Stratec-TB: 9.87 vs. 8.86 vs. 19.37 b. BoneJ-TB: 10.54 vs. 11.02 vs. 19.35 c. Sliceo-WS: 12.64 vs. 10.51 vs. 19.35 4. Inter-rater Precision and Reliability for the Sliceo-WS Method: Adults with SCI (n =10) a. RMS-SD: 1.67 mg/cm³ b. RMS-CV%: 5.18% c. ICC: 0.971, 95%CI (0.888, 0.993)
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Section 5.0 – Calcium and Vitamin D3: Diet or Supplements

Evidence Table 5A

Author, Year Study Design Setting	Population Characteristics Sample Size Injury Level AIS Score Injury Etiology Mean Age & Range Duration of Injury % Female Baseline Bone Characteristics Osteoporotic Status		Interventions Comparison Groups Complications	Timeline Data Source Outcomes	Relevant Results
	SCI	Control			
Bauman, 2005 RCT USA PEDro=10	N:19 Level: 12 tetraplegic, 7 paraplegic; all complete AIS: __ Etiology: __ Age: mean 43, SD 11 years Duration: mean 14, SD 10 years % Female: 0% Ambulatory Status: __ Baseline aBMD (g/cm ²): Total leg: mean 1.018, SD 0.240 Osteoporitic Status: __ Pelvic not reported for SCI group.	Control defined as placebo with calcium and vitamin D800. N:21 Level: 5 tetraplegic, 16 paraplegic; all complete AIS: __ Etiology: __ Age: mean 42, SD 14 years Duration: mean 9, SD 9 years % Female: 4.8% Ambulatory status: __ Baseline aBMD (g/cm ²): Total leg: mean 1.045, SD 0.165 Pelvic: mean 0.966, SD 0.216 Osteoporotic Status: __	Intervention: Daily 1-alpha vitamin D2 4 µg or placebo. All received calcium 1300 mg daily and vitamin D800 IU daily. Comparing: baseline vs follow-ups; vitamin D2 group vs placebo group; smokers participants vs non-smokers participants Vitamin D2 Complications: moderate to severe hypercalciuria (4 participants)	Timeline: follow ups every 6 months for 2 years Data Source: clinical examination using DXA, and blood and urinary analysis Outcomes: BMD (leg, and pelvis), and bone resorption biomarkers (serum and urinary calcium, NTx, OC, and P1NP)	1. Leg aBMD (% change from baseline) only significantly increased for the Vitamin D2 group at 6, 12, 18, and 24 months (all p < 0.05), but not in the placebo group. 2. Vitamin D2 group had significantly greater increases in leg aBMD than the placebo group at months 12 and 18. 3. Only vitamin D2 participants who had never smoked had an increase in leg aBMD at 12, 18, and 24 months (all p < 0.05), but vitamin D2 who were current smokers did not. 4. Vitamin D2 group had reductions in urinary NTx from baseline at 30 to 17 nM BCE/mM at 6 months (p < 0.05). Remained reduced with 20 nM BCE/mM at 24 months (p < 0.05). 5. Vitamin D2 smokers did not have statistically significant reductions in urinary NTx while non-smoking counterparts did.
Hatefi, 2018 RCT Iran PEDro=8	Curcumin Group N: 50 Level: 37 paraplegic, 13 tetraplegic AIS: __ Etiology: traumatic Age: mean 44.32±6.73 years Duration: mean 12.34±4.53 months % Female: 30% Ambulatory Status: __ Baseline aBMD (g/cm ²): Femoral neck: 0.713±0.003 Total hip: 0.707±0.01 Osteoporotic Status: __	Control group defined as placebo Control Group N:50 Level: 40 paraplegic, 10 tetraplegic AIS: __ Etiology: traumatic Age: mean 45.66±6.24 years Duration: 11.65±5.32 months % Female: 24% Ambulatory Status: __ Baseline aBMD (g/cm ²): Femoral neck: 0.714±0.001	Intervention: 110 mg/kg/day curcumin for 6 months Comparing: curcumin intervention group vs. placebo control group Complications: monitoring unclear, not reported	Timeline: follow-up after 6 months Data Source: clinical examination using DXA and blood analysis Outcomes: aBMD (femoral neck and total hip), biomarkers (BALP, P1NP, OC, sCTX)	1. Increase in curcumin group aBMD post intervention a. Femoral neck: 0.718±0.002 g/cm ² , p<0.05 b. Total hip: 0.742±0.03 g/cm ² , p<0.05 2. aBMD difference between curcumin group and control group post treatment at femoral neck (0.718±0.002 g/cm ² vs. 0.712±0.003 g/cm ² , p<0.05, respectively) and total hip (0.742±0.03 g/cm ² vs. 0.692±0.016 g/cm ² , p<0.05) 3. Significant biomarker differences between curcumin and control groups: a. BALP: 8.65±0.98 vs. 14.76±1.8 ng/mL, p<0.05, respectively b. sCTX: 0.45±0.07 vs. 1.25±0.14 ng/mL, p<0.05, respectively

		Total hip: 0.713±0.011 Osteoporotic Status: __			c. Osteocalcin: 21.4±3.9 vs. 25.4±5.7 ng/mL, p<0.05, respectively d. P1NP: 60.21±8.05 vs. 72.43±11.01 ng/mL, p<0.05, respectively
Moran de Brito, 2005 RCT Brazil PEDro=6	N: 10 (9 completed) Level: 8 paraplegic, 2 tetraplegic AIS: __ Etiology: traumatic Age: mean 30.9 ± 9.5 years Duration: mean 61, range 13.1-255.7 months % Female: 20% Ambulatory Status: __ BMD: listed below Osteoporotic Status: unclear Lower Extremity BMD (g/cm2): mean 1.02±0.17 T-index: mean -3.71±1.63 Z-index: mean -3.62±1.74 Total BMD (g/cm2): mean 1.10±0.09 T-index: mean -1.40±0.92 Z-index: mean -1.39±0.84	Control defined as daily calcium treatment (500 mg BID) only. N: 9 (8 completed) Level: 4 paraplegic, 5 tetraplegic AIS: __ Etiology: traumatic Age 30.8±9.9 years Duration: mean 38.7, range 22.8-77.5 months % Female: 22.2% Ambulatory Status: unclear BMD: listed below Osteoporotic Status: unclear Lower Extremity BMD (g/cm2): mean 1.07±0.2 T-index: mean 3.10±2.36 Z-index: mean 3.01±2.44 Total BMD (g/cm2): mean 1.12±0.11 T-index: mean 0.94±1.62 Z-index: mean 0.87±1.58	Intervention: Alendronate (10 mg) daily with calcium supplement (500 mg BID) alone for 6 months. Comparing: before vs. after, Alendronate group vs. control group Alendronate Complications: monitored, none reported Withdrawals Reasons (Total 2): treatment non-compliance (1 control, 1 alendronate)	Timeline: May-Sept 2000 Data Source: clinical examination using DXA DXA Model: Lunar Model DPX (Lunar Corp., Madison, WI, USA) Outcomes: BMD(total body, upper-extremity, lower-extremity, trunk), T-index and Z-index (both expressed as mean and SD from standardized population values) LSC: __	Mean variation for the Alendronate group vs. the control group: 1. BMD a. Total (+0.01 vs. -0.01 g/cm2; p = 0.04) b. Lower extremity (+0.01 vs. -0.01 g/cm2; NS) 2. T-Score a. Total (+0.14 vs. -0.16; p=0.04) b. Lower extremity (+0.02 vs. -0.10 g/cm2; NS) 3. Z-score a. Total (+0.21 vs. -0.13; NS) b. Lower extremity (+0.07 vs. +0.05; NS)
Sabour, 2012 RCT Iran PEDro=10	N: 82 people with osteoporotic SCI randomly assigned between treatment and control groups Level: __ AIS: __ Etiology: __ Age: __ Duration: __ % Female: __	Control Group No participant data reported	Intervention: All participants received 1000 mg calcium and 400 IU vitamin D daily. The participants in the treatment group received two MorDHA capsules (435 g of DHA and 65 mg of EPA per day) or two placebo capsules in the control group.	Timeline: not reported Data Source: clinical examination using blood and urinary analysis Outcomes: levels of blood alkaline phosphatase (BAP), RANK ligand (RANKL) and	1. There were no significant differences between the two groups on any outcome (p=0.56) 2. Mean absolute baseline of BAP in MorDHA group and placebo group has been increased (p<0.001) Mean absolute baseline value of OPG was (4/05±0.84 mmol/l) in the MorDHA group and (4/41±1/21 mmol/l) in the placebo group.

Zehnder, 2004b RCT Switzerland PEDro=7	N: 33 (29 completed) Level: T1-L3; paraplegic; complete motor lesion; Frankel Grade A or B AIS: __ Etiology: traumatic Age: mean 38.8 ± 1.5 years Duration: mean 10.8 ± 1.4 years % Female: 0% Ambulatory Status: unclear BMD: listed below Osteoporotic Status: unclear Tibial Diaphysis: Z-score: mean -1.75 ± 0.38 Absolute BMD: 1.152 ± 0.046 Tibial Epiphysis: Z-score: mean -3.35 ± 0.37 Absolute BMD: 0.495 ± 0.040 Hip: Z-score: mean -1.83 ± 0.25 Absolute BMD: 0.732 ± 0.037	Control defined as daily calcium treatment (500 mg) only. N: 32 (26 completed) Level: T1-L3; paraplegic; complete motor lesion; Frankel Grade A or B AIS: __ Etiology: traumatic Age: mean 37.9 ± 2.2 years Duration: mean 9.9 ± 1.7 years % Female: 0% Ambulatory Status: unclear BMD: listed below Osteoporotic Status: unclear Tibial Diaphysis: Z-score: mean -1.27 ± 0.26 Absolute BMD: 1.210 ± 0.031 Tibial Epiphysis: Z-score: mean -3.02 ± 0.31 Absolute BMD: 0.534 ± 0.030 Hip Z-score: mean -2.10 ± 0.12 Absolute BMD: 0.693 ± 0.017	Intervention: Daily alendronate (10mg) with calcium supplement (500mg) daily or calcium supplement alone for 24 months Comparing: baseline vs. follow-ups; alendronate vs. control Alendronate Adverse Events: 1 diarrhea, 1 obstipation, 1 pyrosis, 1 transitory retrosternal pain, 1 dizziness, 1 chronic headaches which ceased after medication stopped Calcium Adverse Events: 1 diarrhea, 1 obstipation, 2 pyrosis, 1 spontaneous hip fracture when standing, 1 stringomyelia All patients with calcium related GI adverse events (4 in each group) were switched to calcium rich diet. Reasons for Withdrawals (Total 10): moved (3 alendronate, 4 calcium), stringomyelia surgery (1 calcium), obstipation (1 calcium), chronic headaches which ceased after medication stopped (1 alendronate) Complications: __	Timeline: Follows every 6 months for up to 2 years Data Source: clinical examination using DXA, blood and urinary analysis DXA Model: QDR 4500A Outcomes: BMD (distal tibial diaphysis and epiphysis, ultraradial radius, radial shaft, total hip, lumbar spine), bone resorption biomarker (DPD to Cr ratio), bone formation biomarker (OC, total ALP) LSC: __	2 Year Results: - BMD were significantly higher in the calcium group (alendronate vs. control): - Tibial distal epiphysis (-2.0% vs. -10.8%; p=0.017) - Tibial distal diaphysis (-0.7% vs. -3.9%; p=0.019) - Total hip (+0.43% vs. -4.1%; p=0.037) - Compared to the control group, the alendronate group had a greater decrease in: - Deoxypyridinoline (DPD) to Cr ratio (p=0.022) - OC (p=0.005) - Serum ALP (-25.1 + 4.0 vs. -5.2 + 3.8%; p=0.034) - Compared to baseline, both control and alendronate groups had a significant decrease in OC after 24 months (control: 23.2 vs. 17.4; alendronate: 24.1 vs 13.6; p<0.0001) - Compared to baseline, the control group was not significantly different for DPD to Cr ratio at 18 months (-11.7 ± 6.2%) and serum ALP at 24 months (-5.2 ± 3.8%)
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Section 6.0 –Rehabilitation Therapy

Evidence Table 6A. Data abstraction of studies pertaining to Key Question 6G- Standing

A study's N value represents the number of individuals included in the analysis, unless stated otherwise. A patient may have more than one complication, so complication counts may not be mutually exclusive from each other.

Author, Year Study Design Setting	Population Characteristics Sample Size Injury Level AIS Score Injury Etiology Mean Age & Range Duration of Injury % Female Ambulatory Status Baseline Bone Characteristics Osteoporotic Status		Interventions Comparison Groups Complications	Timeline Data Source DXA/pQCT Model Outcomes LSC	Relevant Results
	Intervention Groups(s)	Control Group(s)			
Alekna, 2008 Prospective Study Lithuania	Standing group N: 27 analyzed Level: 17 paraplegic, 10 tetraplegic AIS: ____ Etiology: ____ Age: mean 34.6 ± 12.4 years Duration: mean 11.3 ± 3.19 weeks % Female: 18.5% Mean leg aBMD (g/cm2): All: 1.356 ± 0.098 Paraplegic: 1.346 ± 0.106 Tetraplegic: 1.373 ± 0.084 Mean pelvis aBMD (g/cm2): All: 1.180 ± 0.142 Paraplegic: 1.174 ± 0.144 Tetraplegic: 1.187 ± 0.146 Mean total body aBMD (g/cm2): All: 1.257 ± 0.079 Paraplegic: 1.262 ± 0.092 Tetraplegic: 1.247 ± 0.05 Ambulation: all standing Osteoporosis: ____	Non-standing group N: 27 analyzed Level: 16 paraplegic, 11 tetraplegic AIS: ____ Etiology: ____ Age: mean 33.7 ± 11.4 years Duration: mean 11.2 ± 3.2 weeks % Female: 18.5% Mean leg aBMD (g/cm2): All: 1.375 ± 0.077 Paraplegic: 1.350 ± 0.051 Tetraplegic: 1.391 ± 0.088 Mean pelvis aBMD (g/cm2): All: 1.176 ± 0.122 Paraplegic: 1.285 ± 0.268 Tetraplegic: 1.151 ± 0.111 Mean total body aBMD (g/cm2): All: 1.260 ± 0.071 Paraplegic: 1.250 ± 0.077 Tetraplegic: 1.271 ± 0.06 Ambulation: non-standing Osteoporosis: ____	Intervention: Daily standing using passive standing frame for 1 hr / day. Comparing: before vs. after; paraplegics vs. tetraplegics Complications: unclear monitoring, not reported Withdrawal Reasons: unrelated health problems (11 participants), significantly changed standing regimen (7 participants), and death due to unrelated sepsis (1 participant)	Timeline: Follow-up at 12 and 24 months (+ 3 months) post SCI. Data Source: Clinical examination using DXA DXA Model: DPX-IQ GE Lunar Outcomes: aBMD (pelvis, legs and total body) LSC: ____	1 Year Results: 1. Leg aBMD decreased in the standing group by 19.62% (95%CI [17%, 22%]) and non-standing groups by 24% (95%CI 21%, 27%). 2. Pelvis aBMD decreased in the standing group by 12.37% (95%CI [9%, 15%]) and non-standing group by 15.22% (95%CI [11%, 21%]). 2 Year Results: 1. Standing group had significantly higher aBMD (g/cm2): a. Legs: 1.018, 95%CI [0.971, 1.055] vs. 0.91, 95%CI [0.87, 0.958] (p=0.0004) b. Pelvis: 1.002, 95%CI [0.960, 1.044] vs. 0.934, 95%CI [0.898, 0.970] (p=0.0144) 2. Total body: 1.116, 95%CI
de Bruin, 1999 RCT Switzerland	All N: 19 Etiology: traumatic % Female: 0% Ambulation: ____ BMD: ____	Control defined as no intervention. N: 6 Level: 2 cervical, 4 thoracic AIS: 3 A, 2 B, 1 D Age: mean 33.7, 19 - 59 years	Intervention: Standing/Walking for 25 weeks. Immobilization Group: 0 - 5 hour loading exercises with standing frame per week	Timeline: Follow ups after 5, 9, 13, 17, 21, and 25 weeks post injury Data Source: clinical examination using pQCT	1. Trabecular BMD of the left tibia was significantly lower for the immobilization group compared to the standing or walking groups. No significant difference between standing or walking group for trabecular vBMD

	Osteoporosis: __ Immobilization Group N: 4 Level: 2 cervical, 1 thoracic, 1 lumbar AIS: 1 A, 2 B, 1 C Age: mean 27.5, 21 – 33 years Duration: __ Standing Group N: 5 Level: thoracic; AIS: 4 A, 1 B Age: mean 35.2, range 25 - 48 years Duration: mean 2, 1-3 weeks Walking Group N: 4 Level: 3 cervical, 1 thoracic AIS: 3 C, 1 D Age: mean 34.8, 22 - 53 years Duration: mean 3.3, 2 - 4 weeks	Duration: 5 weeks	Standing Group: 5+ hour of standing exercises per week Walking Group: 5+ hours of standing and treadmill walking Comparing: before vs. after; each intervention group Complications: vertebral fracture (1 walking), pelvic decubitus (1 standing), and noncompliance (2 standing, 1 immobilization)	pQCT Model: Densi-scan 2000 Outcomes: trabecular vBMD, cortical vBMD LSC: __	2. No significant difference groups for the cortical vBMD.
Dudley-Javoroski, 2012 Longitudinal USA	All N: 42 Etiology: __ Ambulation: __ BMD: __ Osteoporosis: __ High Dose Group N: 7 Level: 6 thoracic, 1 cervical AIS: 7 A Age: mean 25.7, 16 - 37 years Duration: mean 0.8, 0.22-2.05 years % Female: 14.3% Low Dose Group N: 5 Level: 5 thoracic AIS: 4 A 1 B Age: mean 39.6, 34 - 44 years Duration: mean 0.5, 0.21 – 0.68 years	Untrained N: 16 Age: mean 38.9, 18 - 64 years Duration: mean 7.4, 0.19 - 24.23 years % Female: 18.8% Able Bodied Individuals defined as normative control. N: 14 Age: mean 30.5, range 22 - 50 years % Female: 21%	Intervention: 3 doses of bone compressive loads 5x/week for over 3 years. Untrained: 0% body weight load Low Dose: passive standing with 40% body weight load for 30 minutes High Dose: Unilateral quadriceps FES stimulation in supported stance (150% body weight compressive load = “High Dose”) while opposite leg received 40% body weight = “Low Dose”. FES was delivered 60 100-pulse trains at 20 Hz, up to 200 mA, with 5 seconds of rest between trains. Two stimulation bouts completed each session. Comparing: before vs. after; each SCI group	Timeline: Follow ups were 1-6 times over 3-year period. Time Bins (Post SCI): 1. 0 - 0.25 years 2. 0.25 - 0.50 years 3. 0.50 - 0.75 years 4. 0.75 - 1 years 5. 1 - 1.5 years 6. 1.5 - 2 years 7. >2 years Data Source: clinical assessment using pQCT pQCT Model: Stratec XCT 3000 Outcomes: vBMD (proximal tibia, distal tibia and distal femur) LSC: __	Overall: 1. No significant difference between the low dose and untrained groups. Distal Femur Results: 1. High dose group BMD exceeded BMD of the untrained group (p=0.003) and low dose group (p=0.019). 2. Slope of BMD decline over time for untrained/low dose groups (-38.776 mg·cm-3/year) were 3 times greater than the high dose group (-11.970 mg·cm-3/year). 3. At 1 year and 3 years, BMD of untrained/low dose groups was respectively 24.1% and 38.9% lower than the high dose group. Proximal Tibia Results: 1. Cohort dose had no significant effect on vBMD. 2. Slope of vBMD decline over time for untrained/low dose groups (-36.754 mg·cm-3/year) were 25.1% times greater than the high dose group (-29.384 mg·cm-3/year)

	% Female: 0%		Complications: unclear monitoring, not reported		3. At 1 year and 3 years, BMD of untrained/ low dose groups was respectively 21.0% and 22.6% lower than the high dose group. Distal Tibia Results: 4. Cohort dose had no significant effect on vBMD. 5. Slope of BMD decline over time for untrained/low dose groups (-59.537 mg·cm-3/year) were 14.4% times lower than the high dose group (-69.261 mg·cm-3/year) 6. At 1 year and 3 years, BMD of untrained/ low dose groups was respectively 5.5% lower and 37.5% greater than the high dose group.
Dudley-Javoroski, 2013 Longitudinal (Continuation of Dudley-Javoroski, 2012) USA	FES Active Standing Group N: 7 Level: 6 thoracic, 1 cervical AIS: 7 A Etiology: __ Age: mean 25.7, 16 - 37 years Duration: mean 0.8, 0.22-2.05 years % Female: 14.3% Ambulation: __ BMD: __ Osteoporosis: __ Passive Standing Group N: 5 Level: 5 thoracic AIS: 4 A 1 B Etiology: __ Age: mean 39.6, 34 - 44 years Duration: mean 0.5, 0.21 – 0.68 years % Female: 0% Ambulation: __ BMD: __ Osteoporosis: __	Control defined as able-bodied individuals. N: 12 Age: mean 29.1, 22 – 48 years % Female: 25%	Intervention: Active-resisted stance with FES of the quadriceps or passive stance 3x/week for up to 3 years. FES Active Standing: Stimulation was applied unilaterally to the quadriceps for 30 minutes at 20hz for 60 contractions at supramaximal intensity. Compression load on the femur was ~150% of body weight. Passive Standing: Compression load at all knee angles was ~40% of body weight. Comparing: before vs. after; active stance group vs. passive stance group vs. controls Complications: unclear monitoring, not reported	Timeline: Follow ups were 1-6 times over 3-year period. Time Bins (Post SCI): 1. 0 - 0.25 years 2. 0.25 - 0.50 years 3. 0.50 - 0.75 years 4. 0.75 - 1 years 5. 1 - 1.5 years 6. 1.5 - 2 years 7. >2 years Data Source: clinical examination using pQCT pQCT Model: Stratec XCT 3000 Outcomes: trabecular vBMD (12% femur) Low dose and untrained group data was pooled. LSC: __	1. At >2 years of training, distal femur trabecular BMD was higher for the active-resisted stance group than for the passive stance group (p=0.007). 2. Slope of BMD decline in the distal femur for active standing group vs. passive standing group as measured % of non-SCI BMD/year: a. Antero-lateral: -2.214 vs. -4.527 b. Anteromedial: -1.623 vs. -4.301 c. Posterolateral: -2.662 vs. -4.738 d. Posteromedial: -1.287 vs. -3.357 3. At 1.5 years, no quadrant of the femur declined 82.7% of non-SCI BMD. Trabecular BMD was preferentially spared in the posterior quadrants of the femur with active-resisted stance.
Eser, 2003 Prospective Controlled Study Switzerland	N: 21 (19 analyzed) Level: C5-T10; 8 cervical, 11 thoracic AIS: A or B Etiology: traumatic Age: mean 32.9 + 11.5 years Duration: 2 weeks – 3 months % Female: 10.5%	Control defined as standing group. N: 19 Level: C5- T1; 8 cervical, 11 thoracic; AIS: A or B Etiology: traumatic	Intervention: 1. FES and Standing FES-cycling sessions for 3 days per week and 30 min standing session on 2 other days of the week. Stimulation was applied to the	Timeline: Follow up after intervention complete (4 – 9 months after first CT scan) Data Source: clinical examination using CT	1. Both groups had 0-10% decrease in tibial cortical vBMD at 3-10 months. 2. Follow-up vBMD value for both groups was 1.18 + 0.05 g/cm3 (FES+S Group Range: 1.06–1.24 g/cm3; S Group Range: 1.03–1.24 g/cm3) 3. Mean absolute change in vBMD per month (g/cm3):

	Right Tibia Absolute BMD: 1.21 + 0.03 g/cm ³ Ambulation: ____ Osteoporosis: ____	Age: mean 33.8 years, SD 13.0, Range 20 – 60 years Duration: 2 weeks – 3 months % Female: 10.5% Right Tibia Absolute BMD: 1.22 + 0.06 g/cm ³ Ambulation: ____ Osteoporosis: ____	quadriceps, gluteal, and hamstring muscles. Stimulation pulses were set at 0.3 ms, increased and maintained if after 6 sessions 30 mins of cycling could not be achieved with 0 kilopond resistance. Stimulation frequencies were randomly set at 30, 50, and 60 Hz. Stimulation intensities increased randomly up to 140 mA. Participants had progressive training until they could cycle for 30 minutes. 2. Standing Passive standing for 30 min for 5 days/week. Comparing: before vs. after; FES group vs control group FES Withdrawals Reasons (Total 2): no corresponding controls of a comparable age could be found	CT Model: Somatom Plus 4 Outcomes: cortical vBMD of right tibia diaphysis (50% site, and 5cm proximal and distal to the 50% site) LSC: ____	a. FES+S Group: 0.004 + 0.01 b. S Group: 0.008 + 0.01 4. Mean relative vBMD change per month (%): a. FES+S Group: -0.34 + 0.59 b. S Group: -0.66 + 0.83 5. Intergroup differences for absolute and relative vBMD changes were not significant.
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Evidence Table 6B. Data abstraction of studies pertaining to Key Question 6H – Treadmill Training

A study's N value represents the number of individuals included in the analysis, unless stated otherwise. A patient may have more than one complication, so complication counts may not be mutually exclusive from each other.

Author, Year Study Design Setting	Population Characteristics Sample Size Injury Level AIS Score Injury Etiology Mean Age & Range Duration of Injury % Female Ambulatory Status Baseline Bone Characteristics Osteoporotic Status		Interventions Comparison Groups Complications	Timeline Data Source DXA/pQCT Model Outcomes LSC	Relevant Results
	Intervention Group(s)	Control Group(s)			
de Bruin, 1999 RCT Switzerland	All N: 19 Etiology: traumatic % Female: 0% Ambulation: ____ BMD: ____ Osteoporosis: ____	Control defined as no intervention. N: 6 Level: 2 cervical, 4 thoracic AIS: 3 A, 2 B, 1 D	Intervention: Standing/ Walking for 25 weeks. Immobilization Group: 0 - 5 hour loading exercises with standing frame per week	Timeline: Follow ups after 5, 9, 13, 17, 21, and 25 weeks post injury Data Source: clinical examination using pQCT	1. Trabecular BMD of the left tibia was significantly lower for the immobilization group compared to the standing or walking groups. No significant difference between standing or walking group for trabecular vBMD 2. No significant difference groups for the cortical vBMD.

	Immobilization Group N: 4 Level: 2 cervical, 1 thoracic, 1 lumbar AIS: 1 A, 2 B, 1 C Age: mean 27.5, 21 – 33 years Duration: __ Standing Group N: 5 Level: thoracic; AIS: 4 A, 1 B Age: mean 35.2, range 25 - 48 years Duration: mean 2, 1-3 weeks Walking Group N: 4 Level: 3 cervical, 1 thoracic AIS: 3 C, 1 D Age: mean 34.8, 22 - 53 years Duration: mean 3.3, 2 - 4 weeks	Age: mean 33.7, 19 - 59 years Duration: 5 weeks	Standing Group: 5+ hour of standing exercises per week Walking Group: 5+ hours of standing and treadmill walking Comparing: before vs. after; each intervention group Complications: vertebral fracture (1 walking), pelvic decubitus (1 standing), and noncompliance (2 standing, 1 immobilization)	pQCT Model: Densi-scan 2000 Outcomes: trabecular vBMD, cortical vBMD LSC: __	
Giangregorio, 2005 Pre-post Canada	N: 5 (4 completed) Level: C3-C8 AIS: 4 B, 1 C Etiology: traumatic Age: mean 29.6, range 19-40 years Duration: mean 114.2, range 66 - 170 days % Female: 60 % Ambulation: __ Mean BMD (g/cm²): Proximal Femur: 1.025 + 0.1175 Proximal Tibia: mean 0.961 + SD 0.089 Distal Femur BMD (g/ cm²): mean 1.099 + 0.118 Whole Body BMD (g/ cm²): mean 1.194 + 0.030 vBMD (mg/cm³): 60% Femur: mean 794.6 + 20.2 66% Tibia: mean 795.84 + 39.52 Osteoporosis: 1 osteopenic	None	Intervention: Body-weight supported treadmill training for 2x/week for 48 sessions during 6-8 months. Initial sessions were 5 mins and were increased gradually to 10-15 mins in all but 1 participant. Comparing: before vs. after Complications: monitored, none reported	Timeline: Follow up after the 48 sessions. Urinary analysis after 24 sessions as well. Data Source: clinical examination using DXA, CT and urinary analysis DXA Model Hologic 4500A densitometer CT Model: General Electric CTI Scanner; BonAllyse 1.3 Software Outcomes: DXA derived aBMD (hip, distal femur and proximal tibia), CT-derived vBMD (60% femur and 66% tibia), CT- derived bone CSA (60% femur and 66% tibia), and biomarkers (OC and Cr corrected DPD). LSC: __	1. aBMD decreased at almost all lower limb sites by 1.2 - 26.7% for all participants. 2. aBMD decreased at proximal femur by 4.3 - 22.6% for all participants. 3. No consistent changes in bone geometry at distal femur and proximal tibia as derived by CT. 4. DPD levels reduced from 6.5 - 21 times normal ranges at baseline to 2.4 - 10 times. Normal ranges were defined as 3.0–7.4nmol DPD/ mmol Cr for females and 2.3–5.4nmol DPD/ mmol Cr for males. 5. OC remained within normal ranges of 3.7–10. 0 ng/ml for females and 3.4–9.1 ng/ml for males. 6. According to WHO criteria and proximal Femur aBMD, 2 participants became osteopenic, and 1 developed osteoporosis.

Evidence Table 6C. Data abstraction of studies pertaining to Key Question 7E- Standing

A study's N value represents the number of individuals included in the analysis, unless stated otherwise. A patient may have more than one complication, so complication counts may not be mutually exclusive from each other.

Author, Year	Population Characteristics		Interventions	Timeline	Relevant Results
Study Design	Sample Size		Comparison Groups	Data Source	
Setting	Injury Level		Complications	DXA/(p)QCT Model	
	Injury Etiology			Outcomes	
	Mean Age & Range			LSC	
	Duration of Injury				
	% Female				
	Ambulatory Status				
	Baseline Bone Characteristics				
	Osteoporotic Status				
Goktepe, 2008	Group A N: 20 Level: 18 paraplegic, 2 tetraplegic AIS: 18 A, 2 B Etiology: 18 traumatic, 2 non-traumatic Age: mean 29.8 ± 7.68 years Duration: mean 1624 ± 861 days % Female: 25% Ambulation: ____ Mean T-score: Femoral neck: -1.6 ± 1.5 Ward's triangle: -1.3 ± 1.6 Trochanter: -2.3 ± 1.2 Total femur: -2.1 ± 1.3 Osteoporosis: ____	Group C N: 40 Level: 29 paraplegia, 11 tetraplegia; AIS 37 A, 3 B Etiology: 37 traumatic, 3 non-traumatic Age: mean 31.0 ± 6.0 years Duration: mean 1706 ± 750 days % Female: 10% Ambulation: ____ Mean T-score: Femoral neck: -2.0 ± 1.7 Ward's triangle: -1.5 ± 1.9 Trochanter: -2.5 ± 1.5 Total femur: -2.4 ± 1.4 Osteoporosis: ____	Intervention: Group A: Standing ≥ 1 hr per day; Group B: Standing < 1hour per day; Group C: No standing Comparing: BMD in Group A vs. group B vs. group C	Timeline: unclear Data Source: Clinical examination using DXA and patient reported standing levels. DXA Model: Lunar DPX-MD dual-energy x-ray absorptiometer (Lunar Radiation Corporation, Madison, WI) Outcomes: self-reported standing activity, t-score and aBMD (Ward's triangle, femoral neck and trochanter) LSC: ____	1. There was no statistically significant difference between the 3 groups in the aBMD of any of the regions measured. 2. T-scores were decreased for all groups, similarly the differences were not statistically significant for femoral neck, Ward's triangle, trochanter, and total femur. 3. Group A had a higher mean T-score than Groups B and C, and Group B had a higher mean T-score than group C for femoral neck and total femoral measurements, although the differences were not significant.
Cross-sectional Study	Group B N: 11 Level: 9 paraplegic, 2 tetraplegic AIS: 9 A, 2 B Etiology: 9 traumatic, 2 non-traumatic Age: mean 32.1 ± 10.5 years Duration: mean 1502 ± 1659 days % Female: 18% Ambulation: ____ Mean T-Index: Femoral neck: -2.0±1.8 Ward's triangle: -1.5±2.0				
Turkey	Femoral region tests of 4 patients (group C) not analysed due to effects of bilateral heterotopic ossification.				

	Trochanter: -2.2±1.4 Total femur: -2.3±1.6 Osteoporosis: __				
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Evidence Table 6D. Data abstraction of studies pertaining to Key Question 7E- Walking

A study's N value represents the number of individuals included in the analysis, unless stated otherwise. A patient may have more than one complication, so complication counts may not be mutually exclusive from each other.

Author, Year Study Design Setting	Population Characteristics Sample Size Injury Level AIS Score Injury Etiology Mean Age & Range Duration of Injury % Female Ambulatory Status Baseline Bone Characteristics Osteoporotic Status		Interventions Comparison Groups Complications	Timeline Data Source DXA/(p)QCT Model Outcomes LSC	Relevant Results
	Intervention Group(s)	Control Group(s)			
Ogilvie, 1993 Pre-post England	N: 4 Level: all paraplegic AIS: __ Etiology: traumatic Age: 16, 25, 28, 42 years Duration: >1 year % Female: 50 % Ambulation: chairbound BMD: __ Osteoporosis: __	None	Intervention: Reciprocal gait orthosis (RGO). No protocol provided. Orthotic fitting and training to independent regular ambulation (mean 5 months). Reciprocating gait orthosis was used daily on average for 3 hours. Comparing: before vs. after Complications: 1 patient contracted pressure sore which limited RGO usage.	Timeline: 6 month follow-up intervals for ~24, 18-30 months Source: Clinical examination using quantitative computed tomography (100-200 mrem). Outcomes: BMD (femoral neck) LSC: __	1. 3 of 4 patients increased or maintained femoral neck BMD. 2. 3 patients used orthoses for approximately the average use time. 3. 1 patient had restricted use of RGO due to adverse effect.
Thoumie, 1995 Pre-post France	N: 7 Level: T2-T10; paraplegic AIS: __ Etiology: __ Age: mean 31, 26-33 years Duration: mean 29, 15-60 months % Female: 14.3% Ambulation: __ Mean aBMD (g/cm ²): Femoral neck: 0.7, 0.6-0.8 Osteoporosis: __	Age matched control group (not defined) used for Z-Score comparison.	Intervention: Reciprocating gait hybrid orthosis (RGO-II) training program for 2h, 3x/week, 3 - 14 months. After training program, orthosis used at home or as outpatient with same frequency. Comparing: before vs. after Complications: unclear monitoring, not reported	Timeline: 16 months follow-up Data Source: Clinical examination using DPA. Outcomes: aBMD (femoral neck) LSC: __	1. Results showed a significantly decreased aBMD in 4 participants (change > 0.03), increased aBMD in 1 participant, and no change in 2 participants). 2. All SCI participant's femoral neck aBMD were below the age-control population's reference value (Z-score)

Evidence Table 6E. Data abstraction of studies pertaining to Key Question 7G – Treadmill Training

A study's N value represents the number of individuals included in the analysis, unless stated otherwise. A patient may have more than one complication, so complication counts may not be mutually exclusive from each other.

Author, Year Study Design Setting	Population Characteristics Sample Size Injury Level AIS Score Injury Etiology Mean Age & Range Duration of Injury % Female Ambulatory Status Osteoporotic Status Baseline Bone Characteristics		Interventions Comparison Groups Complications	Timeline Data Source DXA/(p)QCT Model Outcomes LSC	Relevant Results
	Intervention Group(s)	Control Group(s)			
Giangregorio, 2006 Pre-post Canada	N: 14 (13 complete) Level: C4-T12; 11 cervical, 3 thoracic; incomplete AIS: 2 B, 12 C Etiology: traumatic Age: mean 27.2, 20-53 years Duration: mean 7.4, 1.2-24 years % Female: 15.4% Ambulation: ____ Mean 66% tibia vBMD: 745.0 ± 87.8 g/cm ³ BMC: 1437.3 ± 281.9 g Cortical vBMD: 851.3 ± 56.4 g/cm ³ Cortical CSA: 297.0 ± 67.5 Mean Mid-femur : vBMD: 770.4 ± 89.0 g/cm ³ BMC: 1673.9 ± 394.7 g vBMDcort: 847.9 ± 48.4 g/cm ³ CSAcort: 361.8 ± 98.1 mm ² Whole Body: BMD: Mean 1.118 ± 0.1 g/cm ² Osteoporosis: Femoral: 8 osteoporosis, 3 osteopenic, 2 normal	Control defined as no intervention. N: 4 (3 complete) Level: C5-T12; 3 cervical, 1 thoracic; AIS: 2B, 2D Etiology: traumatic Age: mean 38, range 32-41 years Duration: mean 14.8, range 3-25 years % Female: 0% Ambulation: ____ BMD: ____ Osteoporosis: ____	Intervention: Body-weight-supported treadmill training (BWSTT), 12 – 15 months. Completed protocol 3x/week for 144 sessions; intensity and duration increased as tolerated Comparing: before vs. after Complications: 1 pressure sore, 1 occasional knee pain Withdrawal reasons (Control): 1 personal reasons Withdrawal Reasons (Intervention): 1 incompliance	Timeline: follow-up after 144 sessions (12-15 months); urinary analysis after 72 sessions Data Source: Clinical examination using DXA, CT and urinary analysis. DXA Model: Hologic 4500A densitometer, Bedford, Mass CT Model: General Electric (GE) CTI Scanner (GE, Milwaukee, Wis.) Outcomes: DXA derived aBMD (hip, distal femur and proximal tibia), CT derived vBMD (60% femur site and 66% tibia site) and bone CSA, bone formation biomarkers (OC) and bone resorption biomarkers (DPD). LSC: ____	BWSTT Group: 1. No significant changes in bone geometry or vBMD after intervention: a. 66% tibia i. vBMD: 727.8 ± 71.4 g/cm ³ ii. BMC: 1384.2 ± 251.1 g iii. CSAcort: 291.0 ± 60.2 mm ² iv. vBMDcort: 834.2 ± 38.0 g/cm ³ b. 60% femur i. vBMD: Mean 758.1 ± 85.2 g/cm ³ ii. BMC: 1626 ± 363.8 g iii. CSAcort: 353.0 ± 89.8 mm ² iv. vBMDcort: 840.9 ± 43.4 g/cm ³ 2. OC remained at the high end of normal ranges of 3.7–10.0 ng/ml for females and 3.4–9.1 ng/ml for males. 3. DPD levels were elevated at baseline with 13.8 ± 18.1 nmol DPD/mmol Cr and remain elevated with 12.5 ± 15.3 nmol DPD/mmol Cr after 144 sessions. No significant difference between baseline, 72 and 144 sessions. 4. Whole-body BMD decreased to 1.094 ± 0.1 g/cm ² (p=0.006). Control Group: 1. Only 1 participant had a reduction in proximal femur BMD, 2 had reductions in the proximal tibia BMD, and all 3 had reductions in distal femur BMD by 0.9 – 8.6%.

Evidence Table 6F. Data abstraction of studies pertaining to Key Question 6H- FES

A study's N value represents the number of individuals included in the analysis, unless stated otherwise. A patient may have more than one complication, so complication counts may not be mutually exclusive from each other.

Author, Year Study Design Setting	Population Characteristics Sample Size Injury Level AIS Injury Etiology Mean Age & Range Duration of Injury % Female Ambulatory Status Baseline Bone Characteristics Osteoporotic Status		Interventions Comparison Groups Complications	Timeline Data Source DXA/pQCT Model Outcomes LSC	Relevant Results
	Intervention Group(s)	Control Group(s)			
Eser, 2003 Prospective Controlled Study Switzerland	N: 21 (19 analyzed) Level: C5-T10; 8 cervical, 11 thoracic AIS: A or B Etiology: traumatic Age: mean 32.9 + 11.5 years Duration: 2 weeks – 3 months % Female: 10.5% Right Tibia Absolute BMD: 1.21 + 0.03 g/cm ³ Ambulation: __ Osteoporosis: __	Control defined as standing group. N: 19 Level: C5- T1; 8 cervical, 11 thoracic; AIS: A or B Etiology: traumatic Age: mean 33.8 years, SD 13.0, Range 20 – 60 years Duration: 2 weeks – 3 months % Female: 10.5% Right Tibia Absolute BMD: 1.22 + 0.06 g/cm ³ Ambulation: __ Osteoporosis: __	Intervention: 1. FES and Standing. FES-cycling sessions for 3 days per week and 30 min standing session without FES on 2 other days of the week. Stimulation was applied to the quadriceps, gluteal, and hamstring muscles. Stimulation pulses were set at 0.3 ms, increased and maintained if after 6 sessions 30 mins of cycling could not be achieved with 0 kilopond resistance. Stimulation frequencies were randomly set at 30, 50, and 60 Hz. Stimulation intensities increased randomly up to 140 mA. Participants had progressive training until they could cycle for 30 minutes. 2. Standing Passive standing for 30 min for 5 days/week. Comparing: before vs. after; FES group vs control group FES Withdrawals Reasons (Total 2): no corresponding controls of a comparable age could be found	Timeline: Follow up after intervention complete (4 – 9 months after first CT scan) Data Source: clinical examination using CT CT Model: Somatom Plus 4 Outcomes: cortical vBMD of right tibia diaphysis (50% site, and 5cm proximal and distal to the 50% site) LSC: __	1. Both groups had 0-10% decrease in tibial cortical vBMD at 3-10 months. 2. Follow-up vBMD value for both groups was 1.18 + 0.05 g/cm ³ (FES+S Group Range: 1.06–1.24 g/cm ³ ; S Group Range: 1.03–1.24 g/cm ³) 3. Mean absolute change in vBMD per month (g/cm ³): a. FES+S Group: 0.004 + 0.01 b. S Group: 0.008 + 0.01 4. Mean relative vBMD change per month (%): a. FES+S Group: -0.34 + 0.59 b. S Group: -0.66 + 0.83 5. Intergroup differences for absolute and relative vBMD changes were not significant.

Lai, 2010 Prospective controlled Study Taiwan	N: 12 Level: 5 cervical, 7 thoracic AIS: 12 A Etiology: ___ Age: mean 28.9 + 5.3 years Duration: mean 35.3 + 6.1 days, % Female: 16.7 % Mean aBMD (g/cm2) Femoral Neck: 0.927, + 0.189 Distal Femur: 1.003 + 0.064 Ambulation: ___ Osteoporosis: ___	Controls were not explicitly defined. N: 12 Level: 5 cervical, 7 thoracic AIS: 12 A Etiology: ___ Age: mean 28.2 + 5.7 years Duration: mean 34.9 + 8.0 days % Female: 16.7 % Mean aBMD (g/cm2) Femoral Neck: 0.913 + 0.097 Distal Femur: 1.003 + 0.110 Ambulation: ___ Osteoporosis: ___	Intervention: FES-cycling 3x/week for 3 months, followed by 3 months of no FES cycling. Stimulation was applied bilaterally to the quadriceps and hamstrings. Stimulation pulses were 300 μsec long delivered at 20 Hz. Participants cycled with minimal resistance for as long as possible then cycling time was gradually increased up to 30 min. Comparing: before vs. follow-ups; FES vs control	Timeline: Follow ups at 3 and 6 months Data Source: clinical examination using DXA DXA Model: XR 36 WB; Norland XR-36 scanner research software Outcomes: aBMD (right femoral neck and distal femur) LSC: ___	6 Months Results Normalized to Baseline (FES group vs. Control group; all N.S.): 1. Femoral Neck: 90.869 + 1.061% vs. 90.251 + 1.019% 2. Distal Femur: 90.986 + 0.845 vs. 86.539 + 0.971% 6 month compared to 3 month results: 1. Femoral neck aBMD had decreased (both p<0.05) a. FES group from 0.884 + 0.171 g/cm2 to 0.842 + 0.168 g/cm2 b. Control group from 0.867 + 0.095 g/cm2 to 0.825 g/cm2 + 0.092 2. Distal Femur aBMD had decreased (both p<0.05): a. FES group from 0.981 + 0.063 g/cm2 to 0.913 + 0.058 g/cm2 b. Control group from 0.936 + 0.103 g/cm2 to 0.868 g/cm2 + 0.097 3. No significant between group differences in the absolute BMD decrease at either site.
Lambach, 2018 Pre-post California, USA	N: 4 Level: C7- T10; 1 cervical, 3 thoracic AIS: 2 A, 2 B Etiology: traumatic Age: mean 32.5 + 8.5 years Duration: mean 12.5 + 2.65 months % Female: 0% Ambulation: ___ BMD: ___ Osteoporosis: ___	None	Intervention: 90 FES sessions over 9 – 12 months, each session lasting from 30 – 60 mins with up to 30 min of active training time. Muscle Conditioning: Seated FES leg extension/ flexion exercises were used. Stimulation was applied to one quadriceps and the hamstrings of the contralateral limb. Stimulation pulses were 450 μs delivered at 40 Hz, with an intensity of 0 -120 mA. Stimulation lasted 5 s followed by 1 s of rest. Same protocol was applied to the opposite limb. Once the participant was capable of 30 min of FES muscle conditioning, maintaining and full knee extension then they progressed to FES rowing. FES Rowing: Stimulation was applied bilaterally to the quadriceps and hamstrings. Movement involved leg extension first followed by flexion of the arms when the legs reached mid- to near-extension. Participants started off with short intervals (1 – 3 mins) then they progressed to 30 continuous minutes. Comparing: before vs. after Complications: initial mild autonomic dysreflexia (3 participants) and shoulder discomfort (3 participants)	Timeline: Follow ups at baseline, after 30, 60 and 90 exercise sessions Data Source: Clinical examinations using the pQCT pQCT Model: XCT3000, Stratec; XCT 6.00B software Outcomes: trabecular vBMD (4% femur and 4% tibia) BMC, and total vBMD LSC: ___	Trabecular vBMD of Distal Femur Results: 1. Bone stimulus correlated with change in vBMD (p=0.017; R2=0.452). 2. Average number of weekly training sessions attended correlated with change in vBMD (p<0.001; R2=0.700) Baseline vs. Session 30 3. All participants declined (Range: -5% to -11% of baseline). Session 30 vs. Session 60 4. 2 participants had a reduced rate of vBMD loss from -7% to -3% and from -5% to 0%. 5. 2 participants had a 6% and 8% increase in trabecular vBMD. Session 30 vs. Session 60 6. 3 participants experienced little or no vBMD loss in the distal femur (Range: -1% to +2%). 7. 1 participant had a return of bone loss of -10%. Trabecular vBMD of tibia Results: 1. Similar trend as femur trabecular BMD loss. BMC and total BMD results were not reported.

Evidence Table 6G. Data abstraction of studies pertaining to Key Question 6I - NMES

A study's N value represents the number of individuals included in the analysis, unless stated otherwise. A patient may have more than one complication, so complication counts may not be mutually exclusive from each other.

Author, Year Study Design Setting	Population Characteristics Sample Size Injury Level AIS Score Injury Etiology Mean Age & Range Duration of Injury % Female Ambulatory Status Baseline Bone Characteristics Osteoporotic Status		Interventions Comparison Groups Complications	Timeline Data Source DXA/pQCT Model Outcomes LSC	Relevant Results
	Intervention Group(s)	Control Group(s)			
Arija-Blázquez, 2014 RCT Spain	N: 7 (5 completed) Level: T4 – T12; all paraplegic AIS: ____ Etiology: traumatic Age: mean 41.7 + 12 years Duration: mean 5.5 + 1.1 weeks % Female: 0% Ambulation: ____ BMD (g/cm2) Whole Hip: 0.92 + 0.16 Femoral Neck: 0.79 + 0.14 T-Score Whole Hip: -0.97 + 1.66 Femoral Neck: -1.55 + 1.49 Osteoporosis: ____	Control training was the same except current amplitude was set at 0 mA. N: 5 (3 completed) Level: T4 – T12; all paraplegic AIS: ____ Etiology: traumatic Age: mean 36 + 13.6 years Duration: mean 5.8 + 1.7 weeks % Female: 0% Ambulation: ____ BMD (g/cm2) Whole Hip: 1.08 + 0.03 Femoral Neck: 0.96 + 0.15 T-Score Whole Hip: 0.48 + 0.39 Femoral Neck: 0.28 + 1.67 Osteoporosis: ____	Intervention: Electrical stimulation training for 47 minutes, 5 days/week for 14 weeks. Stimulation was applied to the rectus femoris, vastus medialis and vastus lateralis in supinr. Stimulation pulses were 200 µs long delivered at 30 Hz with an intensity of up to 140 mA. Amplitude was adjusted in the Treatment group to elicit similar isometric torque during the 14 weeks. One session consisted of a total of 80 muscle contractions elicited over 47 minutes. Contractions were divided into sets of 10 with 60-second rest in-between. Every 2 sets, knee angle was changed throughout 10°, 35°, 60°, and 85° (0° full extension). Comparing: before vs. after; electrical stimulation vs. control Withdrawal Reasons (Total 4): surgical intervention unrelated to study (1 control), pressure ulcer unrelated to study (1 electrical stimulation), early hospital discharge (1 electrical stimulation), and voluntary discharge (1 control)	Timeline: Follow up after 14 week intervention Source: clinical examination using blood analysis Outcomes: Serum OC and CTx	1. No significant changes from baseline for biomarkers for either group. a. Electrical stimulation Group: b. Serum OC increased by 51.5 + 50.5% (pre: 10.64 ± 5.5 ng/ml). c. Serum CTx decreased by 26.4 + 38% (pre: 1.26 ± 0.6 ng/ml). d. Control Group: e. Serum OC increased by 27.7 + 57% (pre: 6.63 ± 2.5 ng/ml). f. Serum CTx decreased by 28.1 + 26% (pre: 0.93 ± 0.1 ng/ml). 2. No significant between group differences in biomarker changes.
Clark, 2007 Pre-Post Australia	N: 23 (13 completed) Level: 13 tetraplegic (C1-T1), 10 paraplegic (T2-T12) AIS: 23 A - B Etiology: 21 traumatic, 2 non-traumatic Age: mean 28.6 + 8.6 years	Control not defined. N: 10 (7 completed) Level: 2 tetraplegic (C1-T1), 8 paraplegic (T2-T12) AIS: 8 A - B, 2 C - D Etiology: 9 traumatic, 1 non-traumatic Age: mean 31 + 10.7 years	Intervention: Low-intensity NMES to leg muscles for 15 mins, 2x a day for 5 days per week for 5 months. Stimulation was applied unilaterally at quadriceps femoris and anterior tibial motor points to elicit isotonic and un-resisted muscle repetitions for 4s followed by 8s of rest. Stimulated limb was supported at the knee in 20° flexion. Comparing: before vs. after; NMES group vs. control group	Timeline: 1997 – 2001 Follow ups were at 6 and 12 weeks, and 3 and 6 months post injury. Data Source: clinical examination using DXA by blinded operator	1. aBMD % change from baseline to 6 months (Control Group vs. NMES Group; all N.S.): a. Total body: -1.9 + 1.9 vs. -3.0 + 2.6 b. Lower extremity: -4.7 + 2.7 vs. -7.1 + 3.1 c. Femoral neck: -6.5 + 6.3 vs. -11.6 + 6.1

	Duration: ~3 weeks % Female: 10% Ambulation: __ BMD: __ Osteoporosis: __	Duration: ~3 weeks % Female: 9.1% Ambulation: __ BMD: __ Osteoporosis: __	Complications: small haematoma that resolved with rest (1 FES participant) Withdrawals Reasons (Total 13): medical complication unrelated to treatment (4 NMES, 1 control), protocol violation (3 NMES, 2 control), time constraint (2 NMES), and lost to follow-up (1 NMES)	DXA Model: GE-Lunar Expert XL; Expert 1.92 software Outcomes: aBMD (total body, left lower extremity region, left femoral neck, and left proximal femur)	d. Proximal femur: -8.4 + 7.6 vs. 10.8 + 4.6
Dudley-Javoroski, 2008a Case-control USA	N: 3 Level: T4, T4, T9 AIS: 3 A Etiology: __ Age: 28, 26, 36 years Duration: > 16 weeks % Female: 0% Ambulation: __ BMD: __ Osteoporosis: __ Participants originally from Shields et al. 2006b.	Controls defined as matched SCI and non-SCI participants who received no treatment. Matched SCI controls further divided into sub-acute (<1 year post SCI) and chronic SCI for comparison. SCI Controls N: 9 Level: 5 cervical, 4 thoracic; C5-T11; AIS Score: 6 A, 3 B Age: mean 33.9, range 21 – 72 years Duration: mean 9.26, range 0.3 – 22.5 years % Female: 0% Tibia Trabecular vBMD Chronic SCI: mean 101.3 mg/cm³ Acute SCI: range 190.7 – 294.6 mg/cm³ Non-SCI Controls N: 7 Age: mean 38.1, range 24 – 61 years	Intervention: Unilateral NMES of soleus 5x/week at 15 Hz every 2 s for 120 contractions (8000 contractions/month) for 4.4 to 6 years. Mean estimated compressive loads delivered to the distal tibia were ~1.5 times body weight. Comparing: trained leg vs. untrained leg, soleus trainers vs. (acute and/or chronic) SCI controls vs. non-SCI controls Complications: unclear monitoring, not reported	Timeline: Annual follow up for up to 6 years Data Source: clinical examinations using pQCT pQCT Model: Stratec XCT-2000 or 3000 densitometer Outcomes: trabecular vBMD of distal tibia 4% site LSC: __	Soleus Trainer Results 1. Within the first two year post SCI, tibial vBMD declined by 35%. 2. The absolute between-limb difference for tibial vBMD was Mean 42.5 mg/cm³, Range of 11.4 – 62.8 mg/cm³. This difference was greater than seen in untrained SCI participants (p=0.00013). 3. Tibial BMD was 23.77% higher for the trained limb than the untrained limb, and with continued training history the difference increased to 27.5%. Central Tibial Core Results: 1. Absolute mean difference between-limb trabecular vBMD was 58.2 + 7.6 mg/cm³. 2. Trabecular BMD was 35.4% higher in the trained limb than the untrained limb and with continued training history the difference increased to 40.4%. Posterior vs. Anterior Tibia Trabecular Results: 1. Trained posterior BMD (203.9 mg/cm³) was greater than the anterior BMD (143.0 mg/cm³; p=0.0439) and the chronic SCI (64% difference; p=0.002), but lower than the non-SCI population anterior (247.6 mg/cm³) and posterior trabecular BMD (272.7 mg/cm³). 2. No between-limb difference emerged in the anterior (19.2 mg/cm³ difference; p>0.05). 3. Absolute between-limb posterior BMD differences for the trained was 76.1 mg/cm³, SE 7.2 mg/cm³

Groah, 2010 RCT USA	N: 16 (13 completed) Level: 9 tetraplegic, 7 paraplegic AIS: 15 A, 1 B Etiology: __ Age: mean 31.1 years, Range 18-44 years Duration: mean 35.9 ± 16.9 days % Female: 6.3% Ambulation: __ Mean BMD (g/cm²) Hip: 1.192 ± 0.14 Distal femur: 0.964 ± 0.21 Proximal tibia: 0.964 ± 0.21 Osteoporosis: __	Control defined as usual inpatient SCI care program. N: 10 (8 completed) Level: 3 tetraplegic, 7 paraplegic AIS: 8 A, 2 B Etiology: __ Age: mean 26.2 years, Range 19-71 years Duration: mean 35.9 ± 23.3 days % Female: 30% Ambulation: __ Mean BMD(g/cm²) Hip: 1.185 ± 0.15 Distal femur: 1.107 ± 0.19 Proximal tibia: 1.107 ± 0.19 Osteoporosis: __	Intervention: Usual inpatient SCI care program with or without quadriceps bilaterally NMES (using Complex Motion Stimulator) for 1 hour (or until fatigue) 5 days/week for 6 weeks. Stimulation was applied to the quadriceps, vastus lateralis and vastus medialis motor points. Stimulation pulses were set at 300 us delivered at 25 Hz with an intensity of 0 -125 mA for 5 seconds followed by 5 seconds of rest. Stimulated limb was supported at the knee in 70° flexion. Comparing: before vs. after vs. follow up; NMES group vs. control group Withdrawals Reasons (Total 5, 1 participant for each): death from sepsis, fall related femur fracture, psychological issues, moved, and lost to follow up	Timeline: NMES Group: Follow up immediately after the intervention and 3 month post intervention Control Group: Follow up after 6 weeks, and ~4.5 months Data Source: clinical examination using blood and urinary analysis Outcomes: Serum OC, urinary NTx and 24-hour urine calcium	1. Compared to baseline, serum did not significantly change for serum OC or NTx for either NMES or control group. Urinary calcium results were not reported.
Shields, 2006a Prospective Controlled trial USA	N: 9 (6 analyzed) Level: 2 cervical, 4 thoracic; C5-T10, complete Etiology: __ Age: mean 27.6, range 21 – 43 years Duration: mean 3.2, range 1.9 – 4.2 months Ambulation: __ BMD: __ Osteoporosis: __	Untrained limb was with-in subject control.	Intervention: Unilateral NMES of soleus using isometric plantar flexion protocol for 35min/day (4 bouts with 5-min rest between bouts), 5 days/week, and for a mean of 2.5 years (Range 1.65- 2 years). Within 1 year, participants generated 150% of body weight loads. Comparing: before vs. after; trained leg vs. untrained leg; time bins Complications: unclear monitoring, not reported Reasons for Withdrawals (Total 3, 1 participant for each): increased work commitments, fracture due to ski accident, and death due to respiratory infection	Time Bins: 1. 0 to 6 weeks 2. 6 weeks to 6 months 3. 6 to 12 months 4. 12 to 18 months 5. 18 to 36 months Data Source: clinical examination using DXA DXA Model: Hologic QDR 2000 scanner Outcomes: aBMD (hips and proximal tibial) LSC: __	Overall aBMD Results 1. Trained limb percent decline remained steady for first 1.5 years of study (p<0.05) Hip aBMD Results: 1. Mean percent decline in BMD for Bin 2 was ~ 12%, Bin 3 was 23%, Bin 4 was 30% and Bin 5 was 35%. 2. Compared to Bin 2, percent decline was greater at Bins 3, 4, and 5 (all p<0.05) 3. No significant difference between train and untrained hip in percent decline. Tibia aBMD Results: 1. Percent decline in untrained limb was greater than the trained limb at all time binds (all p<0.05): Bin 2 (8% vs. -3.8%), Bin 3 (17% vs. 3%), Bin 4 (27% vs. 3.4%) and Bin 5 (32% vs. 16%). 2. Percent decline for trained limb at Bin 5 was greater than Bins 2, 3, and 4 (p<0.05)

Shields, 2006b Prospective Controlled trial USA	N: 7 (6 complied) Level: 2 cervical, 5 thoracic; C5- T10; complete AIS: ____ Etiology: ____ Age: mean 29.1, range 21 – 43 years Duration: mean <4.5 months % Female: 0 % Ambulation: ____ BMD: ____ Osteoporosis: ____	Untrained limb was with-in subject control.	Intervention: Unilateral NMES of soleus using isometric plantar flexion protocol for ~30min/day (4 bouts with 5-min rest between bouts), 5 days/week, and for a mean of 2.42 years (Range 1.87 – 3.05 years). Mean estimated compressive loads delivered to the tibia were ~1-1.5 times body weight. Comparing: trained leg vs. untrained leg Complications: unclear monitoring, not reported	Time Bins: 1. 0 to 6 weeks 2. 6 months 3. 12 months 4. 18 months 5. 24 months 6. 30 months Data Source: clinical examination using pQCT pQCT Model: Stratec XCT-20 Outcomes: cortical vBMD of the tibia at the 4%, 38%, and 66% sites and trabecular vBMD of the tibia at 4% site LSC: ____	1. Trabecular BMD at 4% tibia site was 40mg/cm ³ or 31% higher for the trained limb than the untrained limb. 2. No significant differences in cortical BMD of the tibia at the 38% and the 66% sites.
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Evidence Table 6H. Data abstraction of studies pertaining to Key Question 7H – NMES

A study's N value represents the number of individuals included in the analysis, unless stated otherwise. A patient may have more than one complication, so complication counts may not be mutually exclusive from each other.

Author, Year Study Design Setting	Population Characteristics Sample Size Injury Level AIS Score Injury Etiology Mean Age & Range Duration of Injury % Female Ambulatory Status Osteoporotic Status Baseline Bone Characteristics		Interventions Comparison Groups Complications	Timeline Data Source DXA/(p)QCT Model Outcomes LSC	Relevant Results
	Intervention Group	Control Group(s)			
Belanger et al., 2000 Pre-Post Contralateral limb matched and age-matched AB	N: 14 (good compliance) Level: C5 to T6 AIS: A Etiology: ____ Age: 55, 37, 68, 49 years Duration: All > 1.8 yrs (except n=1 of 1.2 yrs) years % Female: 21 % Ambulation: ____	Untrained limb was used as a with-in subject control. AB age-matched group included as normal BMD control	Intervention: Unilateral NMES for quadriceps extension, with one side against increasing resistive load (1 step increments on cybex). ~60'/day, 5 days/week, and for 24 weeks. Goal was to achieve at least 40 nM torque. Comparing: aBMD before vs. after; trained leg vs. untrained leg	Data Source: Clinical examination using DXA. DXA Model: Hologic QDR 2000 scanner Outcomes: aBMD at distal femur, mid-tibia & proximal tibia	1. ~11% increase in distal femur BMD 2. ~10% increase in proximal tibia BMD 3. No change in mid-tibia BMD (p>0.05) 4. Untrained limb BMD not significantly different from trained at beginning and end of training (p>0.05)

controls	BMD: __ Osteoporosis: __		Compliance: Excellent, mean = 93.4% +/- 5.6% (SD). Range = 65-99% Complications: unclear monitoring, not reported	LSC: __	
Shields, 2007 Pre-Post USA	N: 4 (2-3 complied) Level: T1, T6,T5,T7 AIS: A Etiology: __ Age: 55, 37, 68, 49 years Duration: 9.9, 11.8, 12, 2 years % Female: 0 % Ambulation: __ BMD: __ Osteoporosis: __	Untrained limb was used as a with-in subject control.	Intervention: Unilateral NMES of soleus using isometric plantar flexion protocol for ~30min/day (4 bouts with 5-min rest between bouts), 5 days/week, and for 6 to 11 months. Mean estimated compressive loads delivered to the tibia were ~110% body weight. Comparing: aBMD before vs. after; trained leg vs. untrained leg Complications: unclear monitoring, not reported	Data Source: Clinical examination using DXA. DXA Model: Hologic QDR 2000 scanner Outcomes: aBMD at proximal tibia LSC: __	1. For the n=4 aBMD at proximal tibia unchanged after training for trained and untrained limb (p>0.05). 2. For subset of n=2 with training 2.5 x/wk for 11 months limb of 2 subjects had ~0.02g/cm2 gain (~10%) in BMD, NS. 3. Untrained proximal tibia aBMD did not differ from trained limb proximal tibia aBMD either before or after training.

Evidence Table 6I. Data abstraction of studies pertaining to Key Question 7I – FES

A study's N value represents the number of individuals included in the analysis, unless stated otherwise. A patient may have more than one complication, so complication counts may not be mutually exclusive from each other.

Author, Year Study Design Setting	Population Characteristics Sample Size Injury Level AIS Score Injury Etiology Mean Age & Range Duration of Injury % Female Ambulation Status Baseline Bone Characteristics Osteoporotic Status		Interventions Comparison Groups Complications Withdrawal Reasons	Timeline Data Source DXA/(p)QCT Model Outcomes LSC	Relevant Results
	Intervention Group(s)	Control Group(s)			
Ashe, 2010 Case Series Canada	N: 3 Level: C4 – T7; 1 cervical, 2 thoracic AIS: 1 A, 1 B, 1 C Etiology: traumatic Age: mean 33 + 16.4 years Duration: mean 10.8 + 7.3 years % Female: 100 % Ambulation: 3 non-ambulatory used power or	None	Intervention: Computer controlled leg FES-cycling training 3x/week for 6 months, including habituation and training phases. Electrodes on hamstrings, gluteus, and quadriceps; wave pulse of 500 second duration, 60Hz. Phase 1 (habituation): cycle continuously between 35 – 49 rpm for 30 mins for 2 consecutive sessions. Phase 2 (training): Resistance increased with an increment of 1/8 kilopond.	Timeline: measurements at baseline and 6 months Data Source: Clinical examination using DXA and pQCT. DXA Model: Hologic 4500, Bedford, MA pQCT Model: Stratec Medizintechnik XCT 2000, software version 5.50	Bone parameter change from baseline to post-intervention Participant 1 bone parameter change: a. aBMD: i. Left leg: 15.63% ii. Right leg: 7.35% b. 5% tibia vBMD i. Left leg: -1.6% ii. Right leg: -1.1% c. BMC i. Left leg: -5.6% ii. Right leg: -0.4% Participant 2 bone parameter change: a. aBMD:

	manual wheelchairs. BMD: ____ Osteoporosis: ____		Comparing: BMD in pre vs. post Intervention Complications: unclear, not monitored.	Outcomes: aBMD (lower extremity), vBMDtrab (5% tibia), vBMDcort (50% tibia), BMC LSC: 2%	i. Left leg: -1.38% ii. Right leg: 0.83% b. 5% tibia vBMD i. Left leg: 12.5% ii. Right leg: 13.5% c. BMC i. Left leg: 10.8% ii. Right leg: 15.1% Participant 3 bone parameter change: a. aBMD: i. Left leg: 4.79% ii. Right leg: 0.2% b. 5% tibia vBMD i. Left leg: 16.5% ii. Right leg: -0.5% c. BMC i. Left leg: 38.1% ii. Right leg: 2.8%
BeDell, 1996 Pre-post USA	N: 12 Level: C5 – T12; 2 cervical, 10 thoracic; complete AIS: 12A Etiology: traumatic Age: mean 34 + 6 years, range 23-46 Duration: mean 9.7 + SD 5.1 years % Female: 0% Ambulation: ____ Osteoporosis: ____ Mean aBMD (g/cm ²): Femoral neck: 0.78 + 0.14 Ward's triangle: 0.71 + 0.18 Trochanter: 0.61 + 0.08	Controls defined as normative distributions of able-bodied males of a similar age as established in Mazess et al. 1990.	Intervention: 3-phase FES-cycling program. Stimulation Parameters Stimulation pulses were 400 µsec and 10 to 132 mA applied at 30Hz. Phase 1 Quadriceps strengthening using NMES to illicit 45% active knee extension. Trained until participants could lift 3 – 5 pounds. Phase 2 FES-cycling with stimulation applied to quadriceps, gluteus, and hamstrings. Participants progressed until they could cycle for 30 min continuously. Phase 3A FES cycling continuously for 24x 30-mins, 3x/week. Workload adjusted to participant's abilities. Phase 3B Additional 24 sessions of FES cycling with simultaneous arm ergometry for 30-mins (N= 8). Comparing: before vs. after Complications: Unclear, not monitored	Timeline: Follow up after completion of Phase 3A and 3B (~1 year). Source: clinical examination using DXA DXA Model: ____ Outcomes: bilateral BMD (femoral neck, Ward's triangles, and trochanters) LSC: ____	1. BMD was lower for participants than the normative controls at the femoral neck, trochanter, and Ward's triangle (p<0.025). 2. After Phase 3a, there was no significant difference in mean aBMD (g/cm ²): a. Femoral Neck: 0.79 + 0.15 b. Ward's triangle: 0.71 + 0.19 c. Trochanter: 0.64 + 0.15 3. Further training (Phase 3b) did not increase mean aBMD (g/cm ²): a. Femoral Neck: 0.82 + 0.18 b. Ward's triangle: 0.70 + 0.16 c. Trochanter: 0.61 + 0.10

Bloomfield, 1996 Pre-Post USA	N: 9 (7 complete) Level: C5-T7; 5 cervical, 4 thoracic AIS: Frankel: A/B Etiology: traumatic Age: mean 28.2 + 1.8 years Duration: mean 6.0 + 1.2 years % Female: 44.4% Ambulation: __ Mean aBMD (g/cm²) Femoral neck: 0.803 + 0.046 Distal femur: 0.474 + 0.071 Proximal tibia: 0.358 + 0.058 Mean T-Score Femoral neck: -1.55 + 0.41 Distal femur: -3.83 + 0.047 Proximal tibia: -5.21 + 0.52 Osteoporosis: __	Control defined as SCI individuals who stayed sedentary. N: 8 Level: C4- T1; 6 cervical, 2 thoracic AIS: __ Etiology: __ Age: mean 34.4 + 2.5 years Duration: mean 8.3 years + 2.3 % Female: 37.5% Ambulation: __ Mean aBMD (g/cm²) Femoral neck: 0.697 + 0.056 Distal femur: 0.520 + 0.052 Proximal tibia: 0.391 + 0.060 T-Score Femoral neck: -2.40 + 0.46 Distal femur: -3.73 + 0.36 Proximal tibia: -5.16 + 0.58 Osteoporosis: __	Intervention: FES cycling. Part 1 Quadriceps strengthening: Stimulating quadriceps to complete up to 45 leg extensions for 3 sessions/week. Once they could complete 45 in two consecutive sessions, weight was added until they could reach up to 4.5 kg. Part 2 FES cycling: Monophasic stimulation of the quadriceps, hamstrings, and gluteal muscles at 350 ms duration at 30 Hz and up to 130 mA to try and maintain a cycling rate of 50 rpm. Started off at 0W with a goal of reaching 30 mins of continuous cycling. Then resistance was added by 6W the next session. Comparing: before vs. after Complications: 3 participants had mild to moderate hyperreflexia during the first cycle Withdrawals Reasons (Total 2): moved out of state (1 FES group), and time constraints (1 FES group)	Timeline: measurements at baseline, 3, 6, and 9 months Data Source: Clinical examination using DXA. DXA Model: Lunar DPX, Lunar Radiation Corporation; Lunar Version 3.4; adaptation of Lunar anterior-posterior Outcomes: aBMD (femoral neck, distal femur, and proximal tibia) and biomarkers (intact PTH, calcitonin, 25(OH)D, and serum OC. Calcium, HYP, Cr, serum calcium, inorganic phosphate and total ALP in urine samples LSC: __	6 Month Results - Change in mean aBMD from baseline to 6 months (g/cm²) for FES group vs. control group (all N.S.): - Femoral Neck: -0.016 + 0.011 vs. -0.012 + 0.010 - Distal Femur: +0.023 + 0.016 vs. -0.012 + 0.023 - Proximal Tibia: -0.019 + 0.011 vs. -0.015 + 0.020 - Paraplegics who achieved >18W power had a significant 17.8% increase in bone density at the distal femur (+0.095 + 0.026 g/cm²), while quadriplegics who only achieved <12 W of power had no change. - Those who achieved >18W of power did not have a decrease in proximal tibia aBMD, which was experienced by those who only achieved <12 W of power. 9 month Results: - No significant change in mean aBMD from baseline to 9 months (g/cm²) for FES group: - Femoral Neck: -0.031 + 0.012 - Distal Femur: +0.048 + 0.026 - Proximal Tibia: +0.015 + 0.018 For the FES group, mean serum total calcium increased from 2.16 + 0.04 to 2.30 + 0.02 nmol/L (p<0.05).
Carvalho, 2006 Prospective controlled trial Brazil	All N: 21 Level: 4 C4, 4 C5, 9 C6, 3 C7, 1 C8; tetraplegia AIS: __ Etiology: __ Age: mean 32 ± 8 years Duration: mean 66.4 ± 48.23 months % Female: 0% Ambulation: __ BMD: __ Osteoporosis: __ Gait group	Control defined as no intervention. Control group N: 10 Level: incomplete; AIS: B Mean aBMD (g/cm²) Femoral neck: 0.705, 0.422-1.115 Trochanteric area: 0.698, 0.285-1.740 Total femur: 0.734, 0.543-1.156	Intervention: Treadmill gait training (20 minutes, 2x/week, 6 months) with NMES (25 Hz, monophasic rectangular pulses of 300 µs at max 200 V) to quadriceps and tibialis anterior muscles at least 5 months prior to gait training. Comparing: Gait training group vs controls; pre- and post- training. Complications: unclear monitoring, not reported Withdrawal: Total femur not evaluated for 1 patient in gait group, unreported reason. Femoral neck, trochanteric area and total femur not evaluated in 1 control group patient, contracture of the hip.	Timeline: 6 month follow-up. Data Source: Clinical examination by DXA, blood and urine analysis. DXA Model: DPX-ALPHA Lunar Apparatus (DeWitt, MI, USA) Outcomes: aBMD, bone resorption biomarkers (PYD and DPD corrected for Cr), bone formation biomarkers (OC, BALP).	- Significant increase as defined by LSC in bone formation markers after gait training occurred in 9 patients; 8 patients had a decrease in bone resorption markers. - Of the 9 patients with increased bone formation markers, 3 presented with an aBMD increase at most sites; 4 presented loss of aBMD at most sites; 1 maintained aBMD, except for a loss at total femur; 1 maintained aBMD except for gain at femoral neck. - In control group, bone formation markers showed no changes in 3 patients; 2 patients had an increase; while 3 patients had a decrease in bone resorption markers. - Of the 2 patients in control group with increased bone formation markers, 1 presented with an increase and the other with a decrease. - Mean aBMD (g/cm²) at 6 months: - Gait Group - Femoral neck: 0.751, 0.334-1.022

	N: 11 Level: complete Mean aBMD (g/cm ²) Femoral neck: 0.7695, 0.253-1.114 Trochanteric area: 0.588, 0.319-0.723 Total femur: 0.740, 0.608-0.953			LSC: 3.80% femoral neck, 4.59% trochanteric area, 4.15% total femur	ii. Trochanteric area: 0.593, 0.386-0.655 iii. Total femur: 0.690, 0.385-0.831 b. Control Group i. Femoral neck: 0.701, 0.523 - 1.068 ii. Trochanteric area: 0.650, 0.416-1.702 6. Total femur: 0.702, 0.513-1.175
Chen, 2005 Pre-post Taiwan	N: 15 Level: 5 cervical, 10 thoracic AIS: __ Etiology: __ Age: mean 28.67 + 3.9 years Duration: mean 9.3 + 3.9 years % Female: 0% Ambulation: __ Mean aBMD (g/cm ²): Femoral neck: 0.6847 + 0.0648 Distal femur: 0.7177 + 0.0662 Proximal tibia: 0.5533 + 0.0786 Osteoporosis: __	15 age-matched able-bodied male controls. Mean aBMD (g/cm ²): Femoral neck: 0.9232 + 0.1056 Distal femur: 1.1812 + 0.1306 Proximal tibia: 1.0499 + 0.1123	Intervention: FES-cycling exercises with minimal resistance for 30 minutes/day, 5 days/week for 6 months. FES applied to bilateral quadriceps and hamstrings with a pulse frequency, 20 Hz; pulse duration, 300 msec; and maximal intensity, 120mA. Comparing: pre vs. post intervention Complications: unclear, not monitored	Timeline: follow ups at baseline, 6 months, and 6 months post cessation of intervention Data Source: Clinical examination using DXA. DXA Model: XR 36 WB, Nordland Outcomes: aBMD (right femoral neck, distal femur, proximal tibia, and calcaneus). LSC: __	1. At baseline, participants' aBMD at the femoral neck, distal femur and proximal tibia was significantly lower than control. 2. 6 month follow up results: a. Distal Femur: 0.7975 + 0.0703 g/cm ² (p<0.05) b. Proximal Tibia: 0.6248 + 0.0855 g/cm ² (p<0.05) c. Femoral Neck: 0.6695 + 0.0716 g/cm ² (p= NS) 3. 12 month follow-up results (comparing 6 month vs. after 6 months of discontinuing intervention): a. Femoral neck: 0.6249 + 0.0609 g/cm ² (p<0.05) b. Distal femur: 0.7077 + 0.0657 g/cm ² (p<0.05) 4. Proximal tibia: 0.5447 + 0.0765 g/cm ² (p<0.05)
Craven, 2017 RCT Canada	FES Group N: 17 (16 completed) Level: C2-T12 AIS: 6 C, 11 D Etiology: traumatic Age: mean 56.59 + 14 years Duration: median 5 years, IQR 6.6 % Female: 17.6% Ambulation: __ Mean Change aBMD (g/cm ²): Left Total Hip: 0.89 + 0.2 Left Distal Femur: 0.89 ± 0.16 Left Proximal Tibia: 0.71 + 0.18 Mean Change 4% Tbv BMD (mg/cm ³):	Control defined as aerobic (20-25 min, 3-5 Borg; arm or leg bicycling or walking in parallel bars. Treadmill if participants were able to walk unassisted) and resistance (2-3 sets of 12-15 repetitions maximum resistance for muscles capable of voluntary contraction) exercise program. Control Group N: 17 (12 completed)	Intervention: 45 min, 3x/week, 4 months. FES-walking with body weight support group: open-loop FES (8-125 mA, 0-300 µs pulse duration, 20-50 Hz) over the quadriceps, hamstrings, tibialis anterior and gastrocnemius while walking with body weight support. Comparing: BMD and biomarkers in intervention group vs. control group Complications: unclear monitoring, not reported Withdrawals Reasons (Total 6): lost to follow-up (3 dropped out, 1 relocated, and 2 medical removal)	Timeline: between March 2005 – December 2010; follow-up at 4 months and 12 months; biomarkers followed-up at 4 months Data Source: Clinical examination using DXA, pQCT and blood analysis. DXA Model: 4500A, Hologic Inc, Analyzed by ISCD certified technologist pQCT Model: XCT-2000, Stratec Meziertechnik, Stratec XCT-2000 version 5.50 Outcomes: aBMD (left total hip, right distal femur, and right proximal tibia),	Bone Parameter Results: 12 month between group comparison 1. No significant differences for all outcomes at all time points. Mean change at 12 months within- group comparison: 1. FES Group DXA-based aBMD Results (g/cm ²): a. Left Total Hip: 0.88 + 0.2; N.S. b. Left Distal Femur: 0.87 + 0.14; N.S. c. Left Proximal Tibia: 0.69 + 0.17; N.S. pQCT Results (pre vs. post): d. 4% vBMDtrab: 200.51 + 35.89 mg/cm ³ ; p=0.05 e. 38% vBMDtrab: 87.69 + 17.11 vs. 89.06 + 20.43 mg/cm ³ ; N.S. f. 38% vBMDcort: 1089.31 + 37.48 vs. 1082.0 + 36.85 mg/cm ³ ; N.S. g. 38% THlcort: 3.88 + 0.89 vs. 3.75 + 0.78 mm; p=0.04 h. SSI: 2866.34 + 778.20 vs. 2925.79 + 829.38; p=0.05 i. PMI: 58558.03 + 18002.27 vs. 59377.30 + 20364.38 mm ⁴ ; p=0.05

	201.99 + 35.65 Osteoporosis: __	Level: C2-T12 AIS: 7 C, 9 D Etiology: traumatic Age: mean 54.06 + 16.5 years Duration: median 5 years, IQR 18 % Female: 29.4% Ambulation: __ Mean Change aBMD (g/cm²): Left Total Hip: 0.86 + 0.24 Left Distal Femur: 0.81 + 0.18 Left Proximal Tibia: 0.68 + 0.19 Mean Change 4% Tbv vBMD (mg/cm³): 172.91 + 48.10 Osteoporosis: __		vBMD 4% of distal end tibia and 38% of tibial shaft for vBMDcort, vBMDtrab, THlcort, strength-strain index and polar moment of inertia, biomarkers (OC, CTX, Sclerostin), LSC for DXA: 2% for the distal femur 3% for the proximal tibia	Control Group DXA-based aBMD Results (g/cm²): - Left Total Hip: 0.88 + 0.23; p=0.02 - Left Distal Femur: 0.81 + 0.17; N.S. - Left Proximal Tibia: 0.67 + 0.19; N.S. pQCT Results (pre vs. post): 4% vBMDtrab: 169.35 + 51.00 mg/cm³; N.S. 38% vBMDtrab: 88.45 + 27.17 vs. 93.09 + 31.62 mg/cm³; N.S. 38% vBMDcort: 1106.73 + 34.04 vs. 1100.00 + 26.22 mg/cm³; p=0.04 38% THlcort: 4.27 + 1.19 vs. 3.91 + 0.94 mm; N.S. - SSI: 2429.00 + 739.62 vs. 2359.34 + 716.79; N.S. - PMI: 44640.33 + 16882.90 vs. 43774.16 + 17166.62 mm⁴; N.S. Biomarkers - No significant between group changes in OC and CTX after 4 months. - OC concentration significantly increased while CTX concentration significantly increased from baseline in FES-T group only. - Effect size for OC and CTX was small (0.15, and 0.16, respectively) and for sclerostin was medium (0.25). Biomarker mean change, FES group vs. control group: - CTX: 0.039 ± 0.09 vs. 0.024 ± 0.1; N.S. - OC: 1.07 ± 1.92 vs. 0.65 ± 3.44; N.S. - Sclerostin: 1.47 ± 5.28 vs. -1.71 ± 16.90; N.S. FES group results (baseline vs. 4 months): - Mean CTX ng/mL: - Group: 0.26 ± 0.15 vs. 0.24 ± 0.17; p=0.05 - Male: 0.28 ± 0.15 vs. 0.31 ± 0.17; N.S. - Female: 0.17 ± 0.17 vs. 0.22 ± 0.18; N.S. - Mean OC µg/mL: - Group: 16.70 ± 6.51 vs. 17.77 ± 6.23; p=0.02 - Male: 17.7 ± 6.80 vs. 18.87 ± 6.40; N.S. - Female: 12.5 ± 3.04 vs. 13.40 ± 3.20; N.S. - Mean sclerostin pmol/L: - Group: 52.87 ± 16.78 vs. 54.34 ± 20.13; N.S. - Male: 53.27 ± 16.46 vs. 54.55 ± 20.93; N.S. - Female: 51.30 ± 21.81 vs. 53.50 ± 20.66; N.S. Control group results (baseline vs. 4 months): - Mean CTX ng/mL: - Group: 0.24 ± 0.21 vs. 0.27 ± 0.18; N.S. - Male: 0.36 ± 0.23 vs. 0.35 ± 0.20; N.S. - Female: 0.10 ± 0.02 vs. 0.16 ± 0.10; p=0.04 - Mean OC µg/mL: - Group: 20.10 ± 8.33 vs. 20.74 ± 8.62; N.S. - Male: 25.38 ± 7.53 vs. 25.36 ± 7.97; N.S.
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					c. Female: 13.76 ± 3.25 vs. 15.20 ± 6.00; N.S. 3. Mean sclerostin pmol/L: a. Group: 58.28 ± 12.43 vs. 61.06 ± 13.52; N.S. b. Male: 63.60 ± 10.78 vs. 67.26 ± 15.04; N.S. c. Female: 52.96 ± 12.68 vs. 54.86 ± 9.46; N.S.
Frotzler, 2008 Pre-Post Switzerland/ UK	N: 12 (11 Completed) Level: 1 T3, 4 T4, 1 T5, 1 T6, 2 T7, 2 T9; complete AIS: 11 A Etiology: traumatic Age: mean 41.9 ± 7.5 years Duration: mean 11.0 ± 7.1 years % Female: 18.2% Ambulation: ____ Mean BMC (g/cm): 4% femur: 6.21 ± 1.30 4% tibia: 2.14 ± 0.84 38% tibia: 3.51 ± 0.73 4% proximal tibia: 3.59 ± 0.91 Mean vBMDtot (mg/cm³): 4% femur: 157.90 ± 24.17 4% tibia: 166.37 ± 56.98 38% tibia: ____ 4% proximal tibia: 124.44 ± 27.98 Mean CSA_{tot} (mm²): 4% femur: 3924.94 ± 537.72 4% tibia: 1281.65 ± 177.91 38% tibia: 454.01 ± 73.88 4% proximal tibia: 2905.32 ± 546.00 Mean vBMD_{trab} (mg/cm³): 4% femur: 122.10 ± 25.21 4% tibia: 100.52 ± 57.28 38% tibia: ____ 4% proximal tibia: 71.62 ± 25.34	None	Intervention: 3 phase intervention: Phase 1: Isometric bilateral NMES (30-60 mins, 3-5x/week); pulse frequency of 50 Hz, width of 300–400 μs, amplitude 80-150 mA, 1:1 duty cycle set at 6 s on/off; electrodes placed proximally and distally to motor points of gluteus, quadriceps, and hamstring. Phase 2: FES-cycle training (10-60 mins, 3-4x/week, 3 months); pulse frequency of 50 Hz, width of ≤ 500 μs, amplitude adjusted to participant needs; electrodes placed bilaterally on gluteus, quadriceps, hamstrings, as well as triceps surae in 5 participants. Phase 3: High volume FES-cycling (60 mins, 5x/week, 9 months) Comparing: pre vs. post intervention Complications: monitored, none-reported Withdrawals Reasons (Total 1): Foot fracture occurred at 7 months, unrelated to intervention.	Timeline: Measurements at baseline, 6 months, and 12 months. Data Source: Clinical examinations using pQCT pQCT Model: XCT 3000, Stratec Medical; manufacturer's software, version 5.50 E Outcomes: BMC (4% femur; 4%, 38% tibia; 4% proximal tibia), CSA_{tot} (4% femur; 4%, 38% tibia; 4% proximal tibia), BMD_{tot} (4% femur; 4% tibia; 4% proximal tibia), BMD_{trab} (4% femur; 4% tibia; 4% proximal tibia), CSA_{cort} (38% tibia), TH1_{cort} (38% tibia), BMD_{cort} (38% tibia) LSC: ____	Significant results between baseline and 6 months: None-reported Significant results between baseline and 12 months: 1. 4% femur: a. BMD_{trab} increased $14.4 \pm 21.1\%$, $p=0.05$ b. BMD_{tot} increased $7.0 \pm 10.8\%$, $p=0.05$ Significant results between 6 months and 12 months: 1. 4% femur: a. BMD_{trab} increased by $3.1 \pm 3.2\%$, $p=0.016$ b. BMD_{tot} increased $1.3 \pm 1.7\%$, $p=0.041$ c. CSA_{tot} increased $1.2 \pm 1.5\%$, $p=0.001$ All results: 1. 6 month follow-up mean values: a. 4% femur: b. BMC: 6.46 ± 1.19 g/cm i. BMD_{tot}: 166.22 ± 25.14 mg/cm³ ii. CSA_{tot}: 3908.87 ± 560.15 mm² iii. BMD_{trab}: 133.49 ± 23.33 mg/cm³ c. 4% tibia: i. BMC: 2.13 ± 0.82 g/cm ii. BMD_{tot}: 165.24 ± 55.82 mg/cm³ iii. CSA_{tot}: 1283.74 ± 185.51 mm² iv. BMD_{trab}: 99.71 ± 55.64 mg/cm³ d. 38% tibia: i. BMC: 3.52 ± 0.69 g/cm ii. CSA_{tot}: 455.53 ± 74.44 mm² e. 4% proximal tibia: i. BMC: 3.55 ± 0.86 g/cm ii. BMD_{tot}: 123.62 ± 27.46 mg/cm³ iii. CSA_{tot}: 2906.75 ± 592.27 mm² iv. BMD_{trab}: 69.65 ± 23.00 mg/cm³ 2. 12 month follow-up mean values: a. 4% femur: ii. BMC: 6.64 ± 1.30 g/cm iii. BMD_{tot}: 168.41 ± 26.51 mg/cm³ iv. CSA_{tot}: 3958.31 ± 571.72 mm² v. BMD_{trab}: 137.41 ± 25.26 mg/cm³ b. 4% tibia: i. BMC: 2.14 ± 0.84 g/cm ii. BMD_{tot}: 166.91 ± 56.85 mg/cm³ iii. CSA_{tot}: 1279.68 ± 180.07 mm² iv. BMD_{trab}: 100.73 ± 57.28 mg/cm³

	Osteoporosis: __				38% tibia: - BMC: 3.51 ± 0.69 g/cm - CSAtot: 454.45 ± 73.71 mm² d. 4% proximal tibia: - BMC: 3.52 ± 0.88 g/cm - BMDtot: 122.50 ± 26.82 mg/cm³ - CSAtot: 2900.27 ± 571.32 mm² 3. BMDtrab: 69.17 ± 23.02 mg/cm ³
Frotzler, 2009 Pre-Post Switzerland/ UK	N: 5 Level: T4-T7, paraplegic; complete AIS: 5 A Etiology: traumatic Age: mean 38.6 ± 8.1 years, range 27.7-48.4 years Duration: mean 11.4 ± 7.0 years % Female: 20 % Ambulation: __ BMD: __ Osteoporosis: __ Baseline values were published in their previous study (Frotzler et al., 2008). Subjects defined as showing a significant training effect on bone parameters.	None	Intervention: Follow-up on Frotzler et al., 2008, with intention to show the effect of detraining post FES-cycling intervention. 4 participants stopped FES-cycling and 1 reduced training to 30 mins, 2-3x /week, from 60 mins, 5x /week) Comparing: pre- high volume training vs. post detraining/reduced training Complications: Unclear, not monitored.	Timeline: measurements at baseline pre-intervention, post-high volume training, 6 and 12 months post high volume training. Data Source: Clinical examination using pQCT. pQCT Model: XCT 3000, Stratec Medical; manufacturer's software, version 6.0 B Outcomes: 4% femur (BMC, BMDtot, and BMDtrab), 4% tibia (BMC, BMDtot, and BMDtrab) LSC: __	Participants that stopped FES-cycling intervention (n=4): 4% femur (% of bone parameter gained in first 6 months of training that was preserved after 12 months of detraining): - BMDtrab: $73 \pm 13.4\%$ 4% femur (% of bone parameter gained in first 6 months of training that was preserved after 12 months of detraining): - BMDtot: $63.8 \pm 8.0\%$ - BMC: $59.4 \pm 3.9\%$ - Tibia: Bone parameters changed between -1.3-1.6%. Participant with reduced FES-cycling intervention (n=1): 4% distal femur % of bone parameter gain from training that was preserved after 12 months of detraining): - BMDtot: 96.2% - BMDtrab: 95% Tibia: Bone parameters decreased by 1.3-4.8%.
Hangartner, 1994 Pre-post USA	N: 15 (9 FES-cycling, 3 NMES knee extension, 3 both interventions) Level: C5-T10; 6 motor and sensory incomplete AIS: __ Etiology: __ Age at Injury: median 25, 17.1-46 years Duration: mean 6.36, 0.3-15.4 years % Female: __ Ambulation: __ BMD: __ Osteoporosis: __	None	Intervention: 12 weeks of NMES knee extension exercise and/or 12 weeks of FES- cycling 3x/week NMES intervention: Stimulation was applied the over quadriceps motor points. Knee extension sessions were 2 sets of 30 reps and a set of 60 reps with half the weight from the first 2 sets. Weight was progressed when participant completed 3 consecutive sessions, up to a maximum of 15kg. Leg-Cycle Ergometry Stimulation was applied the over the motor points of the quadriceps, hamstrings, and	Timeline: follow up post- intervention (2.8 - 19.4 months) Source: Clinical examination using CT. CT Model: OsteoQuant Outcomes: trabecular, cortical, and subcortical BMD of the proximal and distal tibia	- The regression model BMD loss during the first two years post injury was 51.5% for trabecular, 44.2% for subcortical, and 32.7% for cortical BMD. - For the FES group, there was a 0.2 – 3.3% per year reduction in bone loss than derived from the regression model for all bone parameters at the distal end and for trabecular BMD at the proximal end of the tibia ($p < 0.05$).

			gluteal muscles. To reach a cadence of 50 rpm for 30 mins, stimulation pulses were set at a length of 0.375-ms at 35 Hz with a maximum current of 130 mA. Resistance was modified according to the participant's ability. Comparing: bone loss derived from regression model vs. actual bone loss		
Johnston, 2016 RCT USA	Low-Cadence Group N: 9 (8 Completed) Level: C5 – T6; 2 cervical, 7 thoracic AIS: 6A, 3B Etiology: __ Age: mean 45.9 + 12.2 years Duration: mean 14.1 + 11.6 years, % Female: unclear; 3 Females in this study but did not specify which group they were in. Ambulation: __ Mean Distal Femur aBMD (g/cm2): 0.67 + 0.37 Osteoporosis:	High-Cadence Group N: 8 (7 Completed) Level: C4 – T4; 6 cervical, 2 thoracic AIS: 6A, 2B Etiology: __ Age: mean 38 + 11.8 years Duration: mean 10.8 + 9.6 years % Female: __ Ambulation: __ Mean Distal Femur aBMD (g/cm2): 0.80 + 0.20 Osteoporosis: __	Intervention: Cyclical-FES of the bilateral quadriceps, hamstrings, and gluteal muscles at stimulation levels 250ms, 33Hz, and up to 140mA; low cadence group: 20 RPM, high cadence group: 50 RPM; 56 min cycling with 2 min warm-up and cool-down per session; 3 times per week for 6 months; torque increased incrementally by .14Nm if participant reached 56 mins of target cadence. Comparing: bone characteristics in low-cadence vs. high-cadence groups Complications: monitored, none reported Withdrawal Reasons: personal reasons (2 participants)	Timeline: follow-up at baseline and 6 months Data Source: Clinical Examination using MRI and DXA. MRI Model: Signal 1.5T, custom software DXA Model: Discovery C Outcomes: distal femur aBMD, biomarkers (serum BALP, urine NTX, PTH, 25(OH)D), distal femur trabecular bone micro-architecture, mid-femur cortical bone microarchitecture LSC: __	- Post-intervention distal femur aBMD (g/cm2), N.S.: - Low Cadence group: 0.63 + 0.32; -0.04, 95%CI (-0.10–0.02) - High Cadence group: 0.70 + 0.20; -0.03, 95%CI (-0.07–0.01) - Effect size (Low Cad vs. High Cad): - Distal femur aBMD: d=0.08, N.S. - BALP: d=1.19, p=0.03 - NTx: d=0.74, N.S. 25(OH)D: d=0.18, N.S. - PTH: d=0.74, N.S. - Low-cadence group biomarkers (pre- vs. post-, mean): - Mean BALP (µg/L): 12.9 + 3.6 vs. 10.8 + 3.2; -2.32, 95%CI (-4.10–0.55), p=0.02 - Mean NTx (mg/dL): 53.4 + 25.3 vs. 35.0 + 14.5; 0.66, 95%CI (0.45–0.96), p=0.04 - Mean 25(OH)D (ng/mL): 44.5 + 18.8 vs. 36.2 + 10.0; 0.84, 95%CI (0.69–1.02), p=0.05 - Mean PTH (pg/mL): 27.3 + 11.3 vs. 27.9 + 5.8; 0.61, 95%CI (-7.08–8.29), N.S. - High-cadence group biomarkers (pre- vs. post-, mean): - BALP (µg/L): 13.4 + 4.9 vs. 14.7 + 6.1; 1.33, 95%CI (-1.16–3.82), N.S. - NTx (mg/dL): 52 + 39.7 vs. 43.3 + 21.4; 0.90, 95%CI (0.71–1.14), N.S. 25(OH)D (ng/mL): 35.7 + 3.4 vs. 31.2 + 6.1; 0.86, 95%CI (0.74–1.01), N.S. - PTH (pg/mL): 23.6 + 8.9 vs. 16.7 + 5.0; -6.86, 95%CI (-13.04–0.67), p=0.03 No directionality attributed to effect size calculations.
Leeds, 1990 Pre-post USA	N: 6 Level: C4 - C6 AIS: __ Etiology: traumatic Age: mean 23.7 + 3.5 years Duration: mean 5.2 + 2.6 years % Female: 0 % Ambulation: __ Mean aBMD (g/cm2):	Controls defined as normative distributions of an able-bodied population established in Mazess et al. 1987.	Intervention: 1-month NMES quads strengthening exercise, followed by 6 months of FES-cycling. NMES Stimulation applied through 3 electrodes on anterior thigh. Knee extension sessions were 45 lifts/leg 3x/week. Weight increased by 2 pounds when participants completed the set.	Timeline: follow up post-intervention (~7 months) Data Source: Clinical examination using DPA. DPA Model: __ Outcomes: proximal femur aBMD (femoral neck, Ward's triangle, and	- No significant difference in mean proximal femur aBMD (g/cm2): - Femoral neck: 0.64 + 0.08 - Ward's triangle: 0.52 + 0.10 - Trochanter: 0.44 + 0.08 - Post-intervention, proximal femur aBMD remained below controls (% of normal): - Femoral neck: 66.65 - Ward's triangle: 57.43 - Trochanter: 57.67

	Femoral Neck: 0.65 + 0.05 Ward's triangle: 0.52 + 0.07 Trochanter: 0.46 + 0.06 Osteoporosis: __		FES-Cycling Stimulation applied through electrodes on the buttocks, hamstrings, and anterior thigh. FES-cycling sessions were 3X/week up to 30 mins. Sessions progressed from three 5min rides, three 10min rides, two 15min rides, to a 30min ride. Comparing: before vs. after	greater trochanteric). LSC: __	
Mohr, 1997 Pre-post Denmark	N: 10 (9 completed) Level: 6 C6, 4 T2; complete motor lesion AIS: __ Etiology: __ Age: mean 35.3 + 2.3 years Duration: mean 12.5 + 2.7 years % Female: 20% Ambulation: __ Mean aBMD (g/cm2): Femoral neck: 0.63 + 0.05 Proximal tibia: 0.49 + 0.04 Osteoporosis: __	Controls defined as able bodied individuals with similar age N: 5 Age: __ % Female: 20% Ambulation: __ BMD: __ Osteoporosis: __	Intervention: FES of the quadriceps, hamstrings, and gluteal muscle groups to generate a cycling for 30 min, 3x/week for 12 months, followed by 1x/week for 6 months. Work load was as high as possible. Comparing: before vs. after Complications: unclear, not monitored	Timeline: follow up after 12 and 18 months Data Source: Clinical examination using DXA. DXA Model: Nordland XR 26 MK I Outcomes: BMD (femoral neck and proximal tibia) and bone turnover markers (OC and DPD). LSC: __	1. After 12 months, aBMD was significant greater for the proximal tibia (mean 0.54, SE 0.04 g/cm2; p<0.05) but not the femoral neck (mean 0.61, SE 0.05 g/cm2, N.S.) 2. After 18 month follow up, aBMD for the proximal tibia decreased (mean 0.48, SE 0.02 g/cm2) and returned to baseline. Biomarkers were within normal limits at baseline and did not significantly change with FES.
Morse, 2019 RCT USA	Zoledronate + FES Rowing Group N: 20 (10 analyzed) Level: 8 motor complete AIS: A, B, or C Etiology: __ Age: mean 38.3 ± 13.6 years Duration: mean 8.8 ± 11.1 years % Female: 10% Ambulation: All used wheelchair as primary mode of mobility Mean aBMD (g/cm2) Distal femur: 0.76 ± 0.21 Proximal tibia: 0.76 + 0.25 Femoral neck: 0.82 ± 0.18	FES Rowing Group N: 18 (10 analyzed) Level: __ AIS: A, B, or C Etiology: 7 motor complete Age: mean 38.2 + 11.8 years Duration: mean 14.4 + 14.1 years % Female: 10% Ambulation: All used wheelchair as primary mode of mobility Mean aBMD (g/cm2) Distal femur: 0.83 + 0.36 Proximal tibia: 0.82 + 0.34	Intervention: 12 month FES-rowing-exercise program with or without a 1-time dose of Zoledronate (15 minute infusion of 5 mg/100mg solution). Those with 25(OH)D (<30 ng/mL) deficiency supplemented with weekly 50,000 IU of Ergocalciferol for 8 weeks. All were provided with 1500mg calcium and 1000 IU vitamin D daily. Comparing: before vs. after; Zoledronate + FES rowing group vs. FES rowing group; duration of injury; baseline 25(OH)D levels Zoledronate Infusion Adverse Events: 9 acute-phase reaction following Zoledronate infusion, and 1 hypophosphatemia after infusion Adverse Events (Zoledronate + FES rowing group vs. FES rowing group) Calcium/Vitamin D supplement Related:	Timeline: Oct 2010 – Dec 2014 Source: Clinical examination using DXA, QCT and blood analysis. QCT Models: 128-slice multidetector CT scanner (Definition Flash) DXA Model: Fifth-generation, GE Healthcare iDXA with enCore version 12.3 QCT Sites: epiphysis (0 - 10% segment length), and metaphysis (10 - 20%)	FES Rowing: 1. Gains in CTI and BR at the tibial metaphysis were dose-dependent on total amount of exercise performed (p=0.00-0.04). 2. For BR, ~2.533 kWh of FES rowing work was equivalent to the benefits of a 1-time Zoledronate infusion. Compared to the FES Rowing Group, Zoledronate + FES Rowing group had greater: 1. CBV at the proximal tibial metaphysis by 345 + 109mm3 (p=0.006) and the distal femoral metaphysis by 471 + 225 (p=0.006) and the distal femoral metaphysis by 471 + 225 mm3 (p=0.05). 3. CTI by 0.012 + 0.004 mm at the proximal tibia (p=0.013) and by 0.016 + 0.006 mm at the distal femur (p=0.009) 4. BR by 4.51 + 1.73 at the proximal tibia (p=0.019) and by 5.47 + 2.04 at the distal femur Did not specify percentage of tibia and femur and type of bone No results provided for BMC or DXA –based aBMD

	Total hip: 0.77 + 0.17 Osteoporosis: 3 normal BMD, 3 osteopenia, 4 osteoporosis	Femoral neck: 0.85 + 0.30 Total hip: 0.82 + 0.29 Osteoporosis: 3 normal BMD, 3 osteopenia, 4 osteoporosis	kidney stone (2 vs. 1), constipation or loose stool (0 vs. 2), and fatigue (0 vs. 1) Electrical Stim Related: AD during rowing (3 vs. 0), spontaneous ejaculation during stim (1 vs. 0) Exercise-related: musculoskeletal pain (8 vs. 6), dizziness (2 vs. 3), pressure ulcers (2 vs. 4), tachycardia or palpitation (2 vs. 1), hypotension (1 vs. 1), falling (1 vs. 0), skin irritation from rowing straps (0 vs. 1), and nausea (0 vs. 1) Undetermined cause: increased spasticity (3 vs. 1) and claustrophobia (1 vs. 0) Reason for Withdrawals: lost to follow-up (6 FES participants, 4 Zoledronate + FES participants), injury unrelated to study (2 FES participants, 4 Zoledronate + FES participants), loss of interest in study (5 FES participants, 1 Zoledronate + FES participant), depressive episode (1 Zoledronate + FES participant)	segment length) of the distal femur and proximal tibial metaphysis DXA Sites: distal femur, proximal tibia, femoral neck and total hip Outcomes: blood level of Vitamin D, aBMD, BMC, index vBMC, bone volume, bending strength index (BSI), compressive strength (CSI), cortical thickness index (CTI), and buckling ratio (BR) LSC: __	
Needham-Shropshire, 1997 Pre-post USA	N: 16 Level: T4-T11; paraplegic; complete AIS: __ Etiology: __ Age: mean 28.4 + 6.6 years Duration: mean 4.0 + 3.5 years % Female: 18.8% Ambulation: __ Mean aBMD (g/cm2): Femoral neck: 0.77 ± 0.16 Ward's Triangle: 0.69 ± 0.16 Trochanter: 0.58 ± 0.14 Osteoporosis: __	None	Intervention: Standing and ambulation using Parastep® 1 FNS device (24 Hz, 150 µs pulse width, max intensity of 300mA) for 32 sessions over ~12 week period followed by an optional 8 week extension. Comparing: before vs. after intervention. Complications: monitored, none reported	Timeline: ~12 (N= 16) and ~20 week follow-up (N= 14). Data Source: Clinical examination using DPA. Outcomes: aBMD (femoral neck, Ward's triangle, and trochanter) LSC: __	1. There were no significant changes in aBMD (femoral neck, Ward's triangle, and trochanter) after the 32 training sessions and additional 8 week program. 2. aBMD decreased or maintained in 13 participants at the femoral neck; 11 participants at Ward's triangle; 11 participants at the trochanter 3. 20 week Mean aBMD (g/cm2): a. Femoral Neck: Mean 0.76 ± 0.15 b. Ward's triangle: Mean 0.68 ± 0.16 Trochanter: Mean 0.58 ± 0.15
Pacy, 1988 Pre-post UK	N: 4 Level: T4-6; paraplegia AIS: __ Etiology: 1 haemangio-blastoma, 3 unclear Age: 20-35 years Duration: mean 4,	None	Intervention: 10 weeks of NMES quads strengthening exercise, followed by 32 weeks of FES-cycling. NMES Program: Loads were progressive with a range from 1.4 to 11.4 kg bilateral and were done for 15 mins, 5x/week.	Timeline: Follow up immediately after intervention. Data Source: Clinical examination using CT and DPA. DPA Model: NOVO; BMC	1. No significant changes in BMC for the right femur (mean 3.26, 2.39–4.66 g/cm). 2. No significant changes in distal tibia vBMDtrab (mean 0.15, 0.04–0.15 g/cm3)

	1–8 years % Female: 0 % Ambulation: __ Right Femur Mean BMC (g/cm): 3.34, 2.58 - 4.99 Distal Tibia vBMDtrab (g/cm ³): 0.16, 0.01 – 0.41 Osteoporosis: __		FES Program: Cycling was performed at 50 rpm with a resistance ranging from 0 to 18.75 W and was done for 15 mins, 5x/weeks. Stimulation Parameters: Stimulation pulses were 300 µs and applied at 40Hz. Part 1 was set at 65 – 90V, and Part 2 was set at 80 – 125V. Comparing: before vs. after	Lab 22a CT Model: ISOTOM, custom CT system Outcomes: right femur BMC and distal tibia vBMDtrab LSC: __	
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* State: Conflict of Interest, complication number disclaimer, and other statements of important.

Section 7.0 – Drug Therapy

Evidence Table 7A. Summary of studies using alendronate to prevent bone loss during the acute phase of spinal cord injury.

Author, Year Study Design Setting	Population Characteristics Sample Size Injury Level AIS Score Injury Etiology Mean Age & Range Duration of Injury % Female Ambulatory Status Baseline Bone Characteristics Osteoporotic Status		Interventions Comparison Groups Complications	Timeline Data Source DXA Model Outcomes LSC	Relevant Results
	Intervention Group(s)	Control Group(s)			
Gilchrist, 2007* RCT New Zealand	N: 15 (12 completed) Level: 9 cervical, 1 thoracic, 5 thoraco-lumbar AIS: 10 A, 1 B, 3 C, 1 D Etiology: __ Age: 17-55 years Duration: <10 days % Female: 33.3% Ambulation: 8 wheelchair users, 2 wheelchair users/assisted walking, 3 walking Mean T- Scores: Total Hip: 0.42 Femoral Neck: 0.47 aBMD (g/cm²): Total Hip: mean 1.108 + 0.254 Femoral Neck: mean 1.090 + 0.055	Control defined as placebo treatment. N: 16 (13 completed) Level: 6 cervical, 5 thoracic, 5 thoraco-lumbar AIS: 12 A, 4 B Etiology: __ Age: 17-55 years Duration: <10 days % Female: 25.0% Ambulation: 11 wheelchair users, 4 wheelchair users/assisted walking, 1 walking Mean T- Scores: Total Hip: 0.77 Femoral Neck: 0.76 aBMD (g/cm ²):	Intervention: Weekly 70mg Alendronate or placebo for 1 year. Vitamin D supplementation for those with deficient serum 25(OH)-D (< 50 nmol/L). Comparing: baseline vs. follow-ups; Alendronate vs. placebo Complications (Alendronate vs. placebo): abdominal pain (8 vs. 5), constipation (3 vs. 7), diarrhea (4 vs. 2), dyspepsia (0 vs. 3), nausea (11 vs. 14), and vomiting (1 vs. 5), and other minor adverse events (311 vs. 368) Alendronate Serious Adverse	Timeline: Mar 2001 - Feb 2004 Follow ups at 3, 6, 12, and 18 months post injury Data Source: clinical examination using DXA, ultrasound of non-dominant heel, and blood and urinary analysis DXA Model: Lunar DPX-NT Outcomes: aBMD (total hip, femoral neck) LSC: __	1. At 12-months, compared to the placebo group, aBMD for the Alendronate group was preserved at (all p<0.001): a. Total Hip (-3.3% vs. -20.9%) b. Femoral Neck (+0.3% vs. -16.4%) At 18 months, effects were maintained at all sites except the pelvis (all p<0.001)

	Osteoporosis: ____	Total Hip: mean 1.154 + 0.050 Femoral Neck: mean 1.143 + 0.051 Osteoporosis: ____	Events: 1 UTI, 6 surgical procedures, 2 tendon contractures, and 1 pressure area Placebo Serious Adverse Events: 4 surgical procedures, 3 hypertonia, and 3 syringomyelia Withdrawal Reasons (6 Total): noncompliance (3 Alendronate, 1 placebo), and lose to follow up (2 placebo)		
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Evidence Table 7B. Summary of studies using pamidronate to prevent bone loss during the acute phase of spinal cord injury.

Author, Year Study Design Setting	Population Characteristics Sample Size Injury Level AIS Score Injury Etiology Mean Age & Range Duration of Injury % Female Ambulatory Status Baseline Bone Characteristics Osteoporotic Status		Interventions Comparison Groups Complications	Timeline Data Source DXA Model Outcomes LSC	Relevant Results
	Intervention Group(s)	Control Group(s)			
Bauman, 2005 RCT USA	N: 6 Level: 3 tetraplegic, 3 paraplegic; all motor complete AIS: ____ Etiology: ____ Age: mean 39 + 15 years Duration: mean 41 + 17 days % Female: 33.3% Ambulation: ____ aBMD (g/cm2): Distal Femur: mean 0.957 + 0.167 Proximal Tibia: mean 1.107 + 0.253 Osteoporosis: ____	Control defined as placebo (saline) treatment. N: 5 Level: 2 tetraplegic, 3 paraplegic; all motor complete AIS: ____ Etiology: ____ Age: mean 30 + 8 years Duration: mean 45 + 16 days % Female: 25% Ambulation: ____ aBMD (g/cm2): Distal Femur: mean 1.071 + 0.266 Proximal Tibia: mean 1.089 + 0.205 Osteoporosis: ____	Intervention: IV 60mg pamidronate or placebo given at baseline, 1, 2, 3, 6, 9, and 12-months. All received daily multivitamin with recommended allowance of vitamin D. Comparing: baseline vs. treatment phase vs. follow-up phase; Pamidronate vs. placebo Reasons for Withdrawals (Total 3): not reported Complications: unclear monitoring, none reported	Timeline: Follow-up at 1, 2, 3, 6, 9, 12, 18 & 24 months Data Source: clinical examination by blinded assessors using DXA DXA Model: Lunar DPX Outcomes: aBMD of the distal femur and proximal tibia	Results at completion of 12-months of treatment (Pamidronate vs. placebo; all NS): 1. Distal Femur aBMD: 0.853 ± 0.068 vs. 0.915 ± 0.203 g/cm2 2. Proximal Tibia aBMD: 0.821 ± 0.203 vs. 0.771 ± 0.162 g/cm2

Nance, 1999 Prospective Controlled Trial Canada	N: 14 (12 analyzed) Level: 7 cervical, 6 thoracic, 1 lumbar AIS: 10 A, 4 D Etiology: ____ Age: mean 30.8 + 8.3 years Duration: > 6 weeks % Female: 14.3% Ambulation: 4 ambulatory, 10 non-ambulatory BMD: ____ Osteoporosis: ____	Control defined as no drug treatment. N: 10 (7 analyzed) Level: 5 cervical, 4 thoracic, 1 lumbar AIS: 6 A, 4 D Etiology: ____ Age: mean 35.1 + 10 years Duration: > 6 weeks % Female: 0% Ambulation: 4 ambulatory, 6 non-ambulatory BMD: ____ Osteoporosis: ____	Intervention: Conventional rehab with or without IV 30mg Pamidronate every month for 6-months. Comparing: before vs. follow-ups; Pamidronate vs. control; AIS Score A (non-ambulatory) vs. AIS Score D (ambulatory) Pamidronate Complications: 1 pruritic rash after second infusion (discontinued treatment) Reasons for exclusion (Total 5): Etidronate treatment (3 controls), familial osteoporosis (1 Pamidronate), and IV heparin (1 Pamidronate)	Timeline: DXA Imaging for aBMD was completed at 3, 6, and 12-months post injury. Data Source: clinical examination using DXA DXA Model: Lunar DPX Outcomes: aBMD (hip, distal femur, and proximal tibia) LSC: ____	12-month Results: 1. Lower decline in mean aBMD for the Pamidronate group than the control group (-2.7 vs. -8.1%; p=0.02) 2. Pamidronate group had a lower rate of aBMD loss than the control group for: a. Hips: -0.9% vs. -8.2%; p=0.012 b. Distal Femur: -4.7% vs. -10.8%; p=0.033 3. Lower decline in mean aBMD for ambulatory participants than non-ambulatory participants (-4.6% vs. 15.7%; F = 20, p<0.001). 4. Ambulatory participants had lower rate of aBMD loss than the non-ambulatory group for: a. Distal Femur: -3% vs. 12.5%; p=0.001 b. Proximal tibia: -3.25% vs. -14.3%; p<0.001 Walking pamidronate participants had the best BMD perseveration when compared to other treatment and mobility subgroups (p<0.05).
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Evidence Table 7C. Summary of studies using zoledronate to prevent bone loss during the acute phase of spinal cord injury.

Author, Year Study Design Setting	Population Characteristics Sample Size Injury Level AIS Score Injury Etiology Mean Age & Range Duration of Injury % Female Ambulatory Status Baseline Bone Characteristics Osteoporotic Status		Interventions Comparison Groups Complications	Timeline Data Source DXA Model Outcomes LSC	Relevant Results
	Intervention Group(s)	Control Group(s)			
Bauman, 2015 Prospective Control Study USA	N: 6 Level: 4 paraplegic, 2 tetraplegic AIS: A or B Etiology: ____ Age: mean 25.5 + 9.6 years Duration: mean 82 + 18 days % Female: 16.7 % Ambulation: ____ Mean BMD (g/cm2): Total Hip: 1.125 ± 0.166 Femoral Neck: 1.120 ± 0.163 Distal Femur: 1.102 ± 0.148 Proximal Tibia: 1.274 ± 0.245	Control defined as no intervention provided. N: 7 Level: 3 paraplegic, 4 tetraplegic AIS: A or B Etiology: ____ Age: mean 33 + 11 years Duration: mean 82 + 22 days % Female: 14.3 % Ambulation: ____ Mean BMD (g/cm2): Total Hip: 1.020 ± 0.154	Intervention: Single dose of IV 5mg of Zoledronate with daily 1,250 mg calcium carbonate. Those with vitamin D levels < 20 ng/ml were supplemented with 50,000 IU of vitamin D3 for 5 days then daily 800 IU of vitamin D3. Comparing: baseline vs. follow ups; treatment group vs. control group Zoledronate Complications:	Timeline: Follow ups after 6 and 12-months Data Source: clinical examination using DXA DXA Model: Lunar Prodigy Advance; EnCORE software Outcomes: aBMD (total hip, femoral neck, distal femur, proximal tibia)	6-month Results: 1. Zoledronate group compared to the control group lost less BMD at: a. Total Hip (-3.2 % ± 2.1 vs. -13.9 % ± 5.1; p=0.0006) b. Femoral Neck (-0.5 % ± 3.2 vs. -11.6 % ± 3.9; p<0.0001) 2. No significant between group differences for BMD decline in distal femur (-7.9 % ± 3.4 vs. -2.7 % ± 5.0) or proximal tibia (-10.5 % ± 6.4 vs. -4.8 % ± 6.8). 12-month Results: 1. Zoledronate group compared to the control

	Femoral Neck: 1.120 ± 0.163 Distal Femur: 1.102 ± 0.148 Proximal Tibia: 1.274 ± 0.245 Mean Z-Score: Total Hip: 0.250 ± 1.490 Femoral Neck: 0.233 ± 1.376 Osteoporosis: __	Femoral Neck: 1.040 ± 0.191 Distal Femur: 1.134 ± 0.244 Proximal Tibia: 1.341 ± 0.216 Mean Z-Score: Total Hip: -0.657 ± 0.707 Femoral Neck: -0.386 ± 0.869 Osteoporosis: __	acute flu-like symptoms for 24 – 72 h (6 participants), low grade fever of $100.4 - 102.2^{\circ}\text{F}$ (4 participants), febrile reactions up to 103.8°F (2 participants), and nausea, vomiting and subclinical hypocalcaemia (number not stated)	LSC: Root mean square coefficient of variation percent reported: Total Hip: = + 0.6% Femoral Neck: = + 1.0% Distal Femur: = + 1.9% Proximal Tibia: = + 2.6%	group lost less BMD at: a. Total Hip: $-7.5\% \pm 3.6$ vs. $-20.1\% \pm 9.8$ ($p < 0.01$) b. Femoral Neck: $-1.7\% \pm 5.5$ vs. $-16.7\% \pm 5.2$ ($p = 0.0004$) 2. Zoledronate group compared to the control group lost greater BMD at the distal femur ($-18.5\% \pm 3.9$ vs. $-8.4\% \pm 7.2$; $p = 0.01$). 3. No significant between group differences BMD decline in the proximal tibia BMD ($-20.4\% \pm 8.8$ vs. $-7.9\% \pm 12.3$). 4. LSC for the Zoledronate group was exceeded for the total hip, distal femur and proximal tibia for 100% of participants, and for 50% of participants for the femoral neck. Directionality not indicated. LSC for the control group was exceeded for the total hip and femoral neck for 100% of participants, and distal femur and proximal tibia for 71.4% of participants. Directionality not indicated.
Bubbear, 2011** RCT (Open Label) London, UK	N: 7 (6 completed) Level: 1 cervical, 2 thoracic, 4 lumbar; 5 complete, 2 incomplete AIS: __ Etiology: __ Age: mean 31.6 ± 7.1 years Duration: mean 57.9 ± 16.5 days % Female: 42.9% Ambulation: 2 regained walking during study aBMD (g/cm ²) Total Hip: 1.007 ± 0.098 Femoral Neck: 0.883 ± 0.118 Osteoporosis: __	Control defined as standard nursing/ medical care. N: 7 (5 completed) Level: 2 cervical, 5 thoracic; 6 complete, 1 incomplete AIS: __ Etiology: __ Age: mean 27.0 ± 14.4 years Duration: mean 46.7 ± 18.1 days % Female: 28.6% Ambulation: 1 regained walking during study aBMD (g/cm ²) Total Hip: 1.031 ± 0.054 Femoral Neck: 0.971 ± 0.110 Osteoporosis: __	Intervention: Single dose of IV 4mg Zoledronate or standard nursing/ medical care Comparing: baseline vs. follow-ups; Zoledronate vs. control Zoledronate Complications: myalgia, fever and nasal congestion for 24 hours (5 participants) Reasons for Withdrawals (Total 3): unable to attend within time constraints (1 control), declined further visits (1 control), and 1 moved away (1 Zoledronate)	Timeline: Sep 2003 - Feb 2005 Follow-up after 3, 6, and 12-months. Data Source: clinical examination by unblinded assessors using DXA DXA Model: Hologic QDR-Delphi DXA Outcomes: BMD (hips) LSC: coefficient of variation percent reported: Total Hip: = + 1.2% Femoral Neck: = + 3.2%	12-month Results: 1. Zoledronate group had higher aBMD than the control group: a. Total Hip (+12.4%, $p = 0.005$) b. Femoral Neck (+4.8%; N.S.). 6-month aBMD values were not reported.

Goenka, 2018 RCT India	N: 30 (29 completed) Level: 18 cervical, 11 dorsolumbar; 22 complete, 7 incomplete AIS: ____ Etiology: ____ Age: mean 35.41 + 13.45 years Duration: mean 27.5 + 12.2 days % Female: 17% Ambulation: ____ aBMD (g/cm²): ____ Femoral neck: mean 0.87 + 0.12 Total hip: mean 0.90 + 0.15 Osteoporosis: ____	Control defined as standard nursing and medical treatment. N: 30 (28 completed) Level: 20 cervical, 8 dorsolumbar; 20 complete, 8 incomplete AIS: ____ Etiology: ____ Age: mean 35.57 + 13.12 years Duration: mean 27.6 + 10.6 days % Female: 11% Ambulation: ____ aBMD (g/cm²): ____ Femoral neck: mean 0.93 + 0.13 Total hip: mean 0.95 + 0.10 Osteoporosis: ____	Intervention: Standard care with or without IV 5mg Zoledronate infusion Comparing: before vs. follow ups; Zoledronate vs. control Complications: monitored, none reported	Timeline: Feb 2013 – Jan 2015 Follow ups after 3, 6, and 12-months. Source: clinical examination using DXA DXA Model: Hologic QDR-Delphi DXA Outcomes: aBMD (hip and femoral neck)	6-month Results 1. aBMD results (Zoledronate group vs. control group; g/cm²): a. Total Hip: 0.859 ± 0.129 vs. 0.785 ± 0.085 (p=0.014) b. Femoral Neck: 0.787 ± 0.095 vs. 0.806 ± 0.106 (N.S.) 2. Compared to the Zoledronate group, the control group had a greater loss of aBMD from baseline at the femoral neck (MD -0.13; 95%CI [-0.18, -0.09]; p<0.0001) and total hip (MD -0.16; 95%CI, -0.19 to -0.12, p<0.0001). 12-month Results 1. aBMD results (Zoledronate group vs. control group; g/cm²): a. Total Hip: 0.845 ± 0.125 vs. 0.734 ± 0.074 (p<0.001) b. Femoral Neck: 0.806 ± 0.102 vs. 0.729 ± 0.085 (p=0.014) 2. Compared to the Zoledronate group, the control group had a greater loss of aBMD from baseline at the femoral neck (MD -0.08; 95%CI [-0.12, -0.03]; p=0.002) and total hip (MD -0.12; 95%CI [-0.15, -0.08]; p<0.0001)
Oleson, 2020 RCT USA	N: 10 (8 analyzed) Level: 4 cervical, 6 thoracic AIS: A (converted: B, n=2 and C, n=1) Etiology: ____ Age: mean 35.9 + 12.6 years Duration: 12-21 days % Female: 20% Ambulation: ____ Mean BMD (g/cm²): ____ Total Hip: 0.98 + 0.076; Femoral Neck: 0.86 + 0.078; Distal Femur: 0.88 + 0.092; Proximal Tibia: 0.94 + 0.138 Osteoporosis: none	Placebo defined as infusion of 50ml of normal saline over 15 minutes. N: 5 (5 analyzed) Level: 1 cervical, 4 thoracic AIS: A (converted: B, n=1 and C, n=1) Etiology: ____ Age: mean 30.8 + 9.91 years Duration: 12-21 days % Female: 0% Ambulation: ____ Mean BMD (g/cm²): ____ Total Hip: 1.09 + 0.138; Femoral Neck: 0.98 + 0.178; Distal Femur: 1.01 + 0.128; Proximal Tibia: 1.11 + 0.217 Osteoporosis: none	Intervention: Single infusion of 5mg Zoledronic acid (ZA) or placebo. Comparing: baseline vs. 4 and 12 month follow-up phase; ZA vs. placebo ZA Complications: temperatures greater than 100.6 – 103.2 oF for 2 -24 hours (n=7), acute kidney disease (n=1) Reasons for Withdrawals (Total 4): withdrew from study post intervention (1 participant in ZA group)	Timeline: July 2012 - July 2017 ZA and placebo group followed up 4 and 12-months after initial ZA infusion. Data Source: clinical examination by blinded assessors using DXA and laboratory analysis DXA Model: Hologic Delphi W Outcomes: aBMD (total hip, femoral neck, distal femur, and proximal tibia) LSC: ____	Percent Change in baseline aBMD for the Zoledronate vs. Placebo group at 4 months a. Total Hip: 0.92% vs. -12.0% (p=0.006) b. Femoral Neck: 0.97% vs. -9.4%; (p=0.009) c. Distal Femur: -0.78% vs. -6.75%; (p=0.03) d. Proximal Tibia: -0.24% vs. -8.56% (p=NS) Percent Change in baseline aBMD for the Zoledronate vs. Placebo group at 12 months a. Total Hip: -8.2% vs. -21.3% (p=0.002) b. Femoral Neck: -3.9% vs. -17.0%; (p=0.01) c. Distal Femur: -8.1% vs. -10.0%; (p=NS) d. Proximal Tibia: -4.5% vs. -10.0% (p=NS)

Schnitzer, 2016 RCT USA	N: 7 (6 analyzed) Level: 2 cervical, 5 thoracic AIS: 3 A, 1 B, 1 C Etiology: ____ Age: mean 44.3 + 16.3 years Duration: mean 35.1 + 15.4 days % Female: 0% Ambulation: 1 regained walking during study aBMD (g/cm2) Total Hip: mean 1.084 + 0.107 Femoral Neck: mean 0.944 + 0.126 Osteoporosis: none	Control defined as infusion of dilutant only. N: 9 (6 analyzed) Level: 6 cervical, 3 thoracic AIS: 3 A, 4 B, 2 C Etiology: ____ Age: mean 34.1 + 15.5 years Duration: mean 95.3 + 50 days % Female: 11.1% Ambulation: 1 regained walking during study aBMD (g/cm2) Total Hip: mean 1.000 + 0.138 Femoral Neck: mean 0.899 + 0.160 Osteoporosis: none	Intervention: Single infusion of 5mg Zoledronate or placebo. After 6-months, placebo participants were offered Zoledronate treatment. Comparing: baseline vs. follow-up phase; Zoledronate vs. placebo Zoledronate Complications: temperatures greater than 102oF for 24 -36 hours (n=3) Reasons for Withdrawals (Total 4): withdrew consent prior to intervention (1 participant), and loss to follow-up (3 participants)	Timeline: Jan 2010 - Dec 2012 Follow ups after 3, 6, and 12-months. Zoledronate group followed up every 6-months for up to 2 years with 12-months (n=5) and 24 months (n=4). Placebo participants given Zoledronate infusion followed-up at 18 months (n=3). Data Source: clinical examination by blinded assessors using DXA and blood analysis DXA Model: Hologic QDR 4500A DXA Outcomes: aBMD (total hip, femoral neck, distal femur, and proximal tibia) LSC: ____	- aBMD results at 6-months (Zoledronate group vs. control group; g/cm2): - Left Total Hip: -3.7% vs. -12.3% (p=0.03) - Right Total Hip: 2.2% vs. -8.6%; (p=0.03) - Left Femoral Neck: -1.1% vs. -11.1%; (p=0.02) - Right Femoral Neck: -5.1% vs. -20.0% (p=0.01) - Change in baseline aBMD for the Zoledronate group at 12, 18 and 24 months (if reported): - Left Total Hip: -4.8 + 1.1%, -6.2 + 2.6%, -12.4 + 0.8% - Right Total Hip: -3.1 _ 2.7%, -13.1 + 2.4% - Left Femoral Neck: -0.7 + 4.2%, -1.5 + 2.5%, -4.1 + 2.7% - Right Femoral Neck: -2.6 + 4.1%, -7.8 + 7.5% - Delayed Zoledronate infusion in those with >10% BMD loss after 6-months of placebo resulted in stabilization in total hip and left femoral neck aBMD; however, BMD of left distal femur continued to decline.
Shapiro, 2007* RCT USA	All N: 18 Level: C2 - T12; 5 tetraplegic, 13 paraplegic AIS: 14 A, 4 B Etiology: traumatic Age: mean 30.1 + 14.2 years Duration: > 12 weeks % Female: 22.2% Ambulation: ____ BMD: ____ Osteoporosis: ____ Zoledronate Group N: 8 (8 completed) 4mg Group N: 4 5mg Group N: 4	Control defined as infusion of 50ml of normal saline over 15 minutes. N: 10 (9 completed) Age: mean 28.4 + 9.4 years	Intervention: Single dose IV dose of 4mg Zoledronate or 5mg Zoledronate or placebo. Participants with low serum 25(OH)-D received oral supplementation. Comparing: baseline vs. follow-ups; Zoledronate vs. control Data from participants receiving 4mg or 5mg Zoledronate was combined. Zoledronate Complications: acute febrile myalgic reaction (4 participants) Withdrawal reasons (Total 1): Not stated	Timeline: Follow ups at 6 and 12-months. Data Source: clinical examination using DXA, and blood and urinary analysis DXA Model: Hologic QDR 1000 DXA and GE Lunar Outcomes: BMD of the proximal femur LSC: ____	- Compared to the placebo group, the Zoledronate group had improvements in (all p<0.05): 6-months- aBMD of the femur narrow neck and intertrochanteric region 12-months- BMD of the femur narrow neck

Evidence Table 7D. Summary of studies using denosumab to prevent bone loss during the acute phase of spinal cord injury.

Author, Year	Population Characteristics		Interventions	Timeline	Relevant Results
Study Design	Sample Size		Comparison Groups	Data Source	
Setting	Injury Level		Complications	DXA Model	
	Injury Etiology			Outcomes	
	Mean Age & Range			LSC	
	Duration of Injury				
	% Female				
	Ambulatory Status				
	Baseline Bone Characteristics				
	Osteoporotic Status				
Cirnigliaro, 2020	Denosumab defined as 60 mg of Prolia	Placebo defined as 60 mg of normal saline solution	Intervention: 60 mg of denosumab (BL, 6 month, and 12 month) vs. placebo within 90 days of SCI in individuals with an AIS between A-B	Timeline: March 2015 to June 2019	A significant main effect for time and treatment group-time interaction ($p<0.001$) was observed for the ROI (ROI; DFE, DFM, PTE, FN, and TH), suggesting a sparing of aBMD over time in the denosumab group with a significant loss of aBMD in the placebo group.
RCT	N: 13 (10 analyzed for DXA and biomarkers; 7 analyzed for pQCT) Level: 4 tetra, 6 para AIS: A, n=7; B, n=2; and B converted to C, n=1 Etiology: ____ Age: 33.7 ± 11.3 years Duration: 70.4 ± 18.9 days % Female: 20% Ambulation: ____ Mean BMD (g/cm ²) DFM: 1.187 (1.074-1.300) DFE: 1.557 (1.437-1.675) PTE: 1.071 (0.957-1.186) FN: 1.112 (0.977-1.247) TH: 1.110 (0.978-1.241) Osteoporosis: none	N: 13 (8 analyzed for DXA and biomarkers; 7 analyzed for pQCT) Level: 2 tetra, 6 para AIS: A, n=7; B, n=1 Etiology: ____ Age: 33.9 ± 12.3 years Duration: 76.1 ± 17.7 days % Female: 0% Ambulation: ____ Mean BMD (g/cm²) DFM: 1.162 (0.962-1.362) DFE: 1.565 (1.434-1.696) PTE: 0.994 (0.879-1.109) FN: 1.094 (0.951-1.237) TH: 1.115 (1.012-1.218) Osteoporosis: none	Comparing: Baseline vs. 18 month; denosumab vs. placebo Denosumab Complications: Worsening of psoriasis, was related to study drug; no serious related adverse events were observed (n=1) Reasons for Withdrawals (Total 8): Diagnosis of HO n=5, declined to participate n=1, and medical complications n=2	Data Source: Clinical examination by blinded assessors using DXA and laboratory analysis DXA Model: Lunar Prodigy Advance Outcomes: Primary: aBMD at the DFM and DFE Secondary: aBMD at the PTE, FN, and p TH Exploratory: vBMD at the 4% and 38% distal tibia region LSC: FN = 4.0%; TH = 3.0%; DFM= 3.5%; DFE = 4.0%; and PTE = 5.0%	
USA					Percent Change from baseline in aBMD for the denosumab vs. Placebo group at 18 months: a. DFM: $1.2\% \pm 6.4$ vs. $-17.2\% \pm 14.2$ ($p=0.002$) b. DFE: $1.1\% \pm 7.5$ vs. $-30.0\% \pm 11.9$ ($p<0.001$) c. PTE: $1.7\% \pm 8.2$ vs. $-24.1\% \pm 12.3$ ($p<0.001$) d. TH: $3.3\% \pm 8.7$ vs. $-25.6\% \pm 7.6$ ($p<0.001$)

Evidence Table 7E: Data abstraction of studies pertaining to Key Question 7A - Alendronate

Author, Year Study Design Setting	Population Characteristics Sample Size Injury Level AIS Score Injury Etiology Mean Age & Range Duration of Injury % Female Ambulatory Status Baseline Bone Characteristics Osteoporotic Status		Interventions Comparison Groups Complications	Timeline Data Source DXA Model Outcomes LSC	Relevant Results
	Intervention Group(s)	Control Group(s)			
Moran de Brito, 2005 RCT Brazil	N: 10 (9 completed) Level: 8 paraplegic, 2 tetraplegic AIS: __ Etiology: traumatic Age: mean 30.9 ± 9.5 years Duration: mean 61, 13.1-255.7 months % Female: 20.0% Ambulation: __ Mean Lower Extremity BMD (g/cm2): 1.02 ± 0.17 T-Score: -3.71 ± 1.63 Z-Score: -3.62 ± 1.74 Mean Total Body BMD (g/cm2): mean 1.10 ± 0.09 T-Score: -1.40 ± 0.92 Z-Score: -1.39 ± 0.84 Osteoporosis: __	Control defined as daily calcium treatment (500 mg BID) only. N: 9 (8 completed) Level: 4 paraplegic, 5 tetraplegic AIS: __ Etiology: traumatic Age: mean 30.8 ± 9.9 years Duration: mean 38.7, range 22.8 - 77.5 months % Female: 22.2% Ambulation: __ Mean Lower Extremity BMD (g/cm2): 1.07 ± 0.2 T-Score: 3.10 ± 2.36 Z-Score: 3.01 ± 2.44 Mean Total Body BMD (g/cm2): 1.12 ± 0.11 T-Score: 0.94 ± 1.62 Z-Score: 0.87 ± 1.58 Osteoporosis: __	Intervention: Alendronate (10 mg) daily with calcium supplement (500 mg BID) or calcium supplement alone for 6 months. Comparing: before vs. after, Alendronate group vs. control group Alendronate Complications: monitored, none reported Withdrawals Reasons (Total 2): treatment noncompliance (1 control, 1 Alendronate)	Timeline: May - Sept 2000 Data Source: Clinical examination using DXA. DXA Model: Lunar Model DPX (Lunar Corp., Madison, WI, USA). Outcomes: aBMD (total body, upper-extremity, lower-extremity, trunk), T-score and Z-score (both expressed as mean and SD from standardized population values) LSC: __	Mean variation for the Alendronate group vs. the control group: 1. aBMD a. Total Body: 0.01 vs. -0.01 g/cm2; p=0.04 b. Lower extremity: 0.01 vs. -0.01 g/cm2; NS 2. T-score a. Total Body: 0.14 vs. -0.16; p=0.04 b. Lower extremity: 0.02 vs. -0.10; NS 3. Z-score a. Total Body: 0.21 vs. -0.13; NS Lower extremity: 0.07 vs. 0.05; NS

Zehnder, 2004b RCT Switzerland	N: 33 (29 completed) Level: T1- L3; paraplegic; complete AIS: Frankel: A/B Etiology: traumatic Age: mean 38.8 ± 1.5 years Duration: mean 10.8 ± 1.4 years % Female: 0% Ambulation: __ Mean Tibial Epiphysis: aBMD: 0.495 ± 0.040 g/cm² Z-Score: mean -3.35 ± 0.37 Mean Hip: aBMD: 0.732 ± 0.037 g/cm² Z-Score: -1.83 ± 0.25 Tibial Diaphysis aBMD: 1.152 ± 0.046 g/cm² Z-Score: mean -1.75 ± 0.38 Osteoporosis: __	Control defined as daily calcium treatment (500 mg) only. N: 32 (26 completed) Level: T1- L3; paraplegic; complete AIS: Frankel: A/B Etiology: traumatic Age: mean 37.9 ± 2.2 years Duration: mean 9.9 ± 1.7 years % Female: 0% Ambulation: __ Mean Tibial Epiphysis aBMD: 0.534 ± 0.030 g/cm² Z-Score: -3.02 ± 0.31 Mean Hip aBMD (g/cm²): 0.693 ± 0.017 Z-Score: -2.10 ± 0.12 Mean Tibial Diaphysis aBMD: 1.210 ± 0.031 g/cm² Z-Score: -1.27 ± 0.26 Osteoporosis: __	Intervention: Daily alendronate (10mg) with calcium supplement (500mg) daily or calcium supplement alone for 24 months. Comparing: baseline vs. follow-ups, alendronate vs. control Alendronate Adverse Events: 1 diarrhea, 1 obstipation, 1 pyrosis, 1 transitory retrosternal pain, 1 dizziness, 1 chronic headaches which ceased after medication stopped Calcium Adverse Events: 1 diarrhea, 1 obstipation, 2 pyrosis, 1 spontaneous hip fracture when standing, 1 syringomyelia All patients with calcium related GI adverse events (4 in each group) were switched to a calcium-rich diet. Reason for Withdrawals (Total 10): moved (3 alendronate, 4 calcium), syringomyelia surgery (1 calcium), obstipation (1 calcium), chronic headaches which ceased after medication stopped (1 alendronate)	Timeline: Follow-up measurements every 6 months for up to 2 years. Data Source: Clinical examination using DXA, blood and urinary analysis. DXA Model: QDR 4500A Outcomes: aBMD (distal tibial diaphysis and epiphysis, ultraradial radius, radial shaft, total hip, lumbar spine), bone resorption biomarker (DPD to Cr ratio), bone formation biomarker (OC, total ALP) LSC: __	2 Year Results: - aBMD for following sites for Alendronate group were not significantly different from baseline, but were significantly higher than the calcium group (alendronate vs. control): - Tibial distal epiphysis (-2.0% vs. -10.8%; $p=0.017$) - Tibial distal diaphysis (-0.7% vs. -3.9%; $p=0.019$) - Total hip (0.43% vs. -4.1%; $p=0.037$) - Compared to baseline, both control and alendronate groups had a significant decrease in OC after 24 months (control: 23.2 vs. 17.4; alendronate: 24.1 vs. 13.6; $p<0.0001$) - Compared to baseline, the control group was not significantly different for DPD to Cr ratio at 18 months ($-11.7 \pm 6.2\%$) and serum ALP at 24 months ($-5.2 \pm 3.8\%$). - Compared to baseline, Alendronate group had a decrease in: - DPD to creatine ratio (30.8 ± 5.4 vs. 19.0 ± 2.6 pmol/mmol; $p<0.001$) - Serum ALP ($-25.1 \pm 4.0\%$; $p<0.0001$) - Compared to the control group, the Alendronate group had a greater decrease in: - DPD to Cr ratio ($p=0.022$) - OC ($p=0.005$) Serum ALP (-25.1 ± 4.0 vs. $-5.2 \pm 3.8\%$, $p=0.034$)
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Evidence Table 7F. Data abstraction of studies pertaining to Key Question 7B - Denosumab

A study's N value represents the number of individuals included in the analysis, unless stated otherwise. A patient may have more than one complication, so complication counts may not be mutually exclusive from each other.

Author, Year Study Design Setting	Population Characteristics Sample Size Injury Level AIS Score Injury Etiology Mean Age & Range Duration of Injury % Female Ambulatory Status Baseline Bone Characteristics Osteoporotic Status		Interventions Comparison Groups Complications	Timeline Data Source DXA/(p)QCT Model Outcomes LSC	Relevant Results
	Intervention Group(s)	Control Group(s)			
Gifre, 2016 Post-Test Spain	N: 14 Level: C4-T8; 6 paraplegic, 8 tetraplegic AIS: 12 A, 1 B, 1 C Etiology: traumatic Age: mean 39 + 15 years Duration: mean 15.2 + 4 months % Female: 0% Ambulation: 100% wheelchair users Mean BMD (g/cm²): Femoral neck: 0.751 + 0.085 Total hip: 0.718 + 0.072 Osteoporosis: all osteoporotic	None	Intervention: Denosumab (60 mg) every 6 months for up to a 1 year period. Vitamin D supplementation for those with deficient serum 25(OH)D levels (< 20ng/L). Comparing: before vs. after Complications: monitored, none reported Adverse events: 1 soft tissue after traumatic skin abrasion which was resolved with oral antibiotic therapy, 29 UTIs in 9 patients with no significant difference in UTI frequency before and after starting treatment.	Timeline: June 2010 - Dec 2013 Data Source: Clinical examination using DXA, and blood analysis. DXA Model: Lunar Prodigy, Radiation Corporation Madison, WI Outcomes: aBMD (femoral neck, total hip), bone resorption biomarkers (serum calcium, CTx) bone formation biomarkers (bone specific ALP, PINP), other biomarkers (serum Cr, phosphate, 25(OH)D levels) LSC: __	1. Mean aBMD increased at total hip (+2.4 ± 3.6%; p=0.042), and femoral neck (+3.0 ± 3.6%; p=0.006) 2. Decrease in bone turnover markers: ALP (-42%; p<0.001), P1NP (-58%, p<0.001) and serum CTx (-57%; p=0.002) 3. aBMD changes unrelated to bone turnover markers or 25(OH)D changes.

Evidence Table 7G. Data abstraction of studies pertaining to Key Question 7C - Teriparatide

A study's N value represents the number of individuals included in the analysis, unless stated otherwise. A patient may have more than one complication, so complication counts may not be mutually exclusive from each other.

Author, Year Study Design Setting	Population Characteristics Sample Size Injury Level AIS Score Injury Etiology Mean Age & Range Duration of Injury % Female Baseline Bone Characteristics Ambulatory Status Osteoporosis Status		Interventions Comparison Groups Complications	Timeline Data Source DXA/(p)QCT Model Outcomes LSC	Relevant Results
	Intervention Group(s)	Control Group(s)			
Edwards 2018 RCT North America	TV: N: 21 (18 completed) Level: 48% cervical, 52% thoracic, 0% lumbar AIS: 71% A, 14% B, 10% C, 5% D Etiology: __ Age: mean 46.6 + 15.4 years Duration of injury: 21.1 + 13.4 years % Female: 24% Ambulation: __ BMD: __ Osteoporosis Status: __ TA: N: 20 (20 completed) Level: 25% cervical, 65% thoracic, 10% lumbar Etiology: __ AIS: 70% A, 15% B, 10% C, 5% D Age: mean 47.6 years + 16.3 years Duration of injury: 20.5 + 14.6 years % Female: 15% Ambulation: __ BMD: __ Osteoporosis Status: __ All had low bone mass at	VA: N: 20 (18 completed) Level: 30% cervical, 70% thoracic, 0% lumbar AIS: 70% A, 10% B, 20% C, 0% D Etiology: __ Age: mean 40.9 + 16.4 years Duration of injury: 15.4 + 13.4 years % Female: 30% Ambulation: __ BMD: __ Osteoporosis Status: __ All had low bone mass at the total hip or femoral neck (Z-score < -1.5, T-score < -2.5, or T-score < -2.0) and a history of a fragility fracture	Intervention: Teriparatide 20 µg/day + vibration 10 min/d (TV), or Teriparatide 20 µg/day + sham vibration 10 min/d (TA), or Placebo + sham vibration 10 min/d (VA). All participants given daily Cholecalciferol 1000 IU as a calcium carbonate and vitamin D supplement. Comparing: baseline vs. follow ups Complications: 11.7% patients had a fragility fracture of the femur or tibia during initial RCT (3 TA, 2 TV, and 2 VA). 8% had a lower extremity fragility fracture during the open-label teriparatide extension study (TA and TV). TV Withdrawal Reasons: nursing home changes (1), lost to follow-up (2) VA Withdrawal Reasons: lost to follow-up (2)	Timeline: Jun 2011 – Aug 2015; follow-up after 2 and 6 weeks, and 3, 6, 9 and 12 months. After 12 month RCT, participants were invited to an additional 12 months of open-label Teriparatide and vibration treatment. Source: Clinical examination using DXA, CT imaging and blood analysis. DXA Model: Hologic QDR 4500A (Hologic, Waltham, MA, USA) CT Model: Sensation 64 Cardiac Scanner (Siemens Medical Systems, Forchheim, Germany) at NU/RIC site and Lightspeed VCT (GE Medical Systems, Milwaukee, WI, USA) at Hines sites Outcomes: aBMD (total hip, femoral neck, forearm, whole body), bone resorption biomarkers (CTX, P1NP), bone formation biomarker (BALP), CT analysis of the distal femur and proximal tibia (vBMD of the trabecular bone, and BMC and bone volume of the cortical bone) LSC: __	12 Month Results Relative to Baseline: - TA group had significant changes in: - P1NP (+126%) - CTX (+98.7%) - Bone specific AP (+56.7%) - Femur Metaphyseal cBV (+3.81%), cBMC (+6.71%), and TSI (+3.45%) - Tibia Epiphyseal cBV (+14.3%) and cBMC (+16.2%) - Tibia Metaphyseal cBMC (+3.62%) - Tibia Diaphyseal cBMC (+3.66%) - None of the groups had significant changes in hip, femoral neck, distal femur, and proximal tibia DXA scan results. - TV group had an 1.93% (95%CI [0.65-11.1%]) increase in tibia torsional stiffness. - VA group had an 85.3%, (95%CI [-161--9.58%]) decrease in tibia metaphyseal tBMD. - While Teriparatide exhibited skeletal activity in chronic SCI patients, no clinical benefit is observed. 24 Month Results Relative to Baseline: - None of the groups had significant changes in hip, femoral neck, distal femur, and proximal tibia aBMD. - Increase in hip aBMD from baseline only observed after 24 months Teriparatide treatment: TA (6.7%, 95%CI [3.4-10.1%]) and TV (4.2%, 95%CI [0.4 - 8.1%]). - P1NP and BSAP levels increased significantly in TA (102%; 11.5%), TV (58.0%; 10.9%), and VA (104%; 12.6%) groups. - A significant increase in diaphyseal cBMC was observed in all three groups (TA: 3.36%; TV: 3.73%; VA 4.39%). - Both TV and VA groups experienced significant increases in tibia metaphyseal cBV, cBMC, CSI, and TSI (TV: 5.11%,

	the total hip or femoral neck (Z-score < -1.5, T-score < -2.5, or T-score < -2.0) and a history of a fragility fracture.				7.64%, 14.0%, 6.95%; VA: 2.96%, 6.28%, 11.9%, 6.42%), femur epiphyseal cBV and cBMC (TV: 17.9%, 19.4%; VA: 21.7%, 23.4%), and femur metaphyseal TSI (TV: 8.86%; VA: 6.67%) 6. A significant change in femur diaphyseal cBMC was only observed in TV group (20.0%)
Gordon, 2013 Pre-post USA	N: 12 (11 completed) Level: C1-T10 AIS: 5 A, 3 B, 4 C Etiology: __ Age: mean 34 + 8 years Duration: mean 7.7 years % Female: 16.7% Ambulation: __ Mean aBMD (g/cm2) Left total hip: 0.638 + 0.090 Right total hip: 0.626 + 0.088 Left femoral neck: 0.653 + 0.071 Right femoral neck: 0.615 + 0.085 Osteoporosis: all osteoporotic	None	Interventions: Daily Teriparatide (PTH 1-34) 20 µg, calcium 1000 mg, and vitamin D 1000 IU daily combined with treadmill training 3 times/week (20-40 min stepping time at 1.8 to 2.5 km/h, <50% body weight support) for 6 months. During treadmill training, a Lokomat driven gait orthosis and partial body-weight support (>60%) were utilized. Seven participants chose to remain on drug and supplements for an additional 6 months. Comparing: before vs. follow ups Complications: unclear monitoring, not reported Withdrawal Reasons (Total 1): personal reasons Withdrawal reasons from gait training only: logistical reasons (1), transport difficulties (1)	Timeline: Primary follow ups after 3 and 6; additional follow up at 12 months for all who remained on the drug and supplements and one subject who chose not to continue with drug and supplements. Data Source: Clinical examination using DXA, micro-MRI and blood analysis. DXA Model: Hologic machine; QDR4500A; Hologic Inc, Bedford, MA Outcomes: aBMD (total hip, and femoral neck), micro-MRI of distal tibia (bone volume fraction, surface-to-curve ration, erosion index, and trabecular thickness), bone reabsorption biomarkers (CTx and P1NP) and bone formation biomarkers (OC, and BALP) LSC: __	6 Month Results Compared to Baseline: 1. No significant changes in BMD: a. Left total hip (0.02 + 2.21%) b. Right total hip (0.74 + 2.80%) c. Left femoral neck (-0.28 + 2.69%) d. Right femoral neck (1.83 + 4.5%) 2. Bone volume fraction increased (10.6 + 8.3% (p=0.07) 3. No significant changes in surface-to-curve ration, erosion index, and trabecular thickness. 4. No significant increases in mean bone specific ALP (53.8 + 62.9%), CTx (137.6 + 194.6%) and P1NP (61.4 + 99.3%). 12 Month Results Compared to Baseline: 1. Mean increases in bone specific ALP (105.2 + 71.7%; p=0.03), and P1NP (76.2 + 52.6%; p=0.042). 2. No significant changes in BMD between 6 and 12 months: a. Left total hip (1.68 + 3.12%) b. Right total hip (0.37 + 4.60%) c. Left femoral neck (0.58 + 3.98%) d. Right femoral neck (1.26 + 5.14%) 3. No significant change in CTx (61.9 + 122.2%).

Evidence Table 7H: Data abstraction of studies pertaining to Key Question 7D- Zoledronate

A study's N value represents the number of individuals included in the analysis, unless stated otherwise. A patient may have more than one complication, so complication counts may not be mutually exclusive from each other.

Author, Year Study Design Setting	Population Characteristics Sample Size Injury Level AIS Score Injury Etiology Mean Age & Range Duration of Injury % Female Ambulatory Status Baseline Bone Characteristics Osteoporotic Status		Interventions Comparison Groups Complications	Timeline Data Source DXA/(p)QCT Model Outcomes LCS	Relevant Results
	Intervention Group(s)	Control Group(s)			
Morse, 2019 RCT USA	Zoledronate + FES Rowing Group N: 20 (10 analyzed) Level: 8 motor complete AIS: A, B, or C Etiology: ___ Age: mean 38.3 ± 13.6 years Duration: mean 8.8 ± 11.1 years % Female: 10% Ambulation: All used wheelchair as primary mode of mobility Mean aBMD (g/cm²): Distal femur: 0.76 ± 0.21 Proximal tibia: 0.76 ± 0.25 Femoral neck: 0.82 ± 0.18 Total hip: 0.77 ± 0.17 Osteoporosis: 3 normal BMD, 3 osteopenia, 4 osteoporosis	FES Rowing Group N: 18 (10 analyzed) Level: ___ AIS: A, B, or C Etiology: 7 motor complete Age: mean 38.2 ± 11.8 years Duration: mean 14.4 ± 14.1 years % Female: 10% Ambulation: All used wheelchair as primary mode of mobility Mean aBMD (g/cm²): Distal femur: 0.83 ± 0.36 Proximal tibia: 0.82 ± 0.34 Femoral neck: 0.85 ± 0.30 Total hip: 0.82 ± 0.29 Osteoporosis: 3 normal BMD, 3 osteopenia, 4 osteoporosis	Intervention: 12 month FES-rowing-exercise program with or without a 1-time dose of Zoledronate (15 minute infusion of 5 mg/100mg solution). Those with 25(OH)D (<30 ng/mL) deficiency supplemented with weekly 50,000 IU of Ergocalciferol for 8 weeks. All were provided with 1500mg calcium and 1000 IU vitamin D daily. Comparing: before vs. after; Zoledronate + FES rowing group vs. FES rowing group; duration of injury; baseline 25(OH)D levels Zoledronate Infusion Adverse Events: 9 acute-phase reaction following Zoledronate infusion, and 1 hypophosphatemia after infusion Adverse Events (Zoledronate + FES rowing group vs. FES rowing group) Calcium/Vitamin D supplement Related: kidney stone (2 vs. 1), constipation or loose stool (0 vs. 2), and fatigue (0 vs. 1) Electrical Stim Related: AD during rowing (3 vs. 0), spontaneous ejaculation during stim (1 vs. 0) Exercise-related: musculoskeletal pain (8 vs. 6), dizziness (2 vs. 3), pressure ulcers (2 vs. 4), tachycardia or palpitation (2 vs. 1), hypotension (1 vs. 1), falling (1 vs. 0), skin irritation from rowing straps (0 vs. 1), and nausea (0 vs. 1) Undetermined cause: increased spasticity (3 vs. 1) and claustrophobia (1 vs. 0) Reason for Withdrawals: lost to follow-up (6 FES participants, 4 Zoledronate + FES participants), injury	Timeline: Oct 2010 – Dec 2014 Source: Clinical examination using DXA, QCT and blood analysis. QCT Models: 128-slice multidetector CT scanner (Definition Flash) DXA Model: Fifth-generation, GE Healthcare iDXA with enCore version 12.3 QCT Sites: epiphysis (0 - 10% segment length), and metaphysis (10 - 20% segment length) of the distal femur and proximal tibial metaphysis DXA Sites: distal femur, proximal tibia, femoral neck and total hip Outcomes: blood level of Vitamin D, aBMD, BMC, index vBMC, bone volume, bending strength index (BSI), compressive strength	Compared to the FES Rowing Group, Zoledronate + FES Rowing group had greater: 1. CBV at the proximal tibial metaphysis by 345 + 109mm ³ (p=0.006) and the distal femoral metaphysis by 471 + 225 mm ³ (p=0.05). 2. CTI by 0.012 + 0.004 mm at the proximal tibia (p=0.013) and by 0.016 + 0.006 mm at the distal femur (p=0.009) 3. BR by 4.51 + 1.73 at the proximal tibia (p=0.019) and by 5.47 + 2.04 at the distal femur Did not specify percentage of tibia and femur and type of bone FES Rowing Results: 1. Gains in CTI and BR at the tibial metaphysis were dose-dependent on total amount of exercise performed (p=0.00-0.04). 2. For BR, ~2.533 kWh of FES rowing work was equivalent to the benefits of a 1-time Zoledronate infusion. No results provided for BMC or DXA-based aBMD.

			unrelated to study (2 FES participants, 4 Zoledronate + FES participants), loss of interest in study (5 FES participants, 1 Zoledronate + FES participant), depressive episode (1 Zoledronate + FES participant)	(CSI), cortical thickness index (CTI), and buckling ratio (BR) LSC: __	
Varghese, 2016 RCT India	N: 13 (12 analysed) Level: 3 cervical and upper thoracic, 9 lower thoracic and lumbar AIS: __ Etiology: traumatic Age: mean 37.92 + 8.82 years Duration: mean 13.42 + 6.54 years % Female: 25% Ambulation: 33% ambulant Mean aBMD (g/cm2): Total hip: 0.583 + 0.066 Femoral neck: 0.576 + 0.064 Osteoporosis: __	N: 15 (13 analysed) Level: 2 cervical and upper thoracic, 11 lower thoracic and lumbar AIS: __ Etiology: traumatic Age: mean 38.69 + 12.11 years Duration: mean 11.15 + 7.06 years % Female: 0% Ambulation: 54% ambulant Mean aBMD (g/cm2) Total hip: 0.607 + 0.073 Femoral neck: 0.548 + 0.111 Osteoporosis: __	Intervention: single IV infusion of Zoledronate (4 mg) or placebo (saline) Comparing: placebo vs. treatment, baseline vs. follow-up Zoledronate Complications: flu-like symptoms such as bone pain, fever, fatigue, and rigors (5 participants), and post-injection conjunctival redness (1 participants) Reasons for exclusion from analysis (Total 3): did not repeat DXA scan (1 Zoledronate, 1 control), technical scanning error (1 control)	Timeline: follow-up after 1 year Data Source: Clinical examination using DXA. DXA Model: Discovery W, S/N 70471, version 12.7.3.1 Outcomes: aBMD (hip and forearm) LSC: __	1. Within-group decrease in total hip aBMD in placebo group to 0.491 ± 0.169 g/cm2 (p=0.017), but not in the Zoledronate group with 0.563 ± 0.079 g/cm2. 2. Within-group decreases in femoral neck aBMD in placebo group to 0.480 ± 0.163g/cm2 (p=0.002) and the Zoledronate group to 0.552 ± 0.074 g/cm2 (p=0.044). 3. Significant within-group increases in aBMD of distal third of forearm in placebo from 0.713 ± 0.031 to 0.747 ± 0.028g/cm2 and Zoledronate group from 0.717 ± 0.066 to 0.760 ± 0.072 g/cm2 (both p=0.004). 4. No significant between-group differences in percentage changes of aBMD

Evidence Table 7I: Excluded Studies from Drug Therapy Section 7.0

Author	Year	Treatment	Primary Outcomes
Clodronate			
Minaire	1981	Treatment for 100 days Daily oral 400mg Clodronate (n=7) 1,600mg Clodronate (n=7) Placebo (n=7)	• Distal tibia BMC • Iliac total bone density • Trabecular bone volume • Relative osteoid volume • Trabecular osteoid surfaces • Osteoid thickness index • Trabecular osteoclastic resorption surfaces • Number of osteoclasts/mm2 of bone section • Biomarkers (urinary and serum calcium, HYP, ALP, Cr, serum glutamate oxaloacetic transaminase, serum glutamate pyruvate transaminase, and blood count)

Minaire	1987	Treatment for 100 days Daily oral 400mg Clodronate (n=7) Daily oral 1,600mg Clodronate (n=7) Intravenous or subcutaneous 100iu Salmon Calcitonin 3 times per week (n=20) Oral 20mg/kg Etidronate for 8 weeks then 10mg/kg Etidronate for 4 weeks (n=20) Control Group (n=16)	• Trabecular bone volume • Osteoid parameters • Osteoclast count and eroded surfaces • Biomarkers (urinary and serum calcium, HYP and ALP)
Etidronate			
Pearson	1997	Routine SCI rehabilitation with or without Etidronate treatment. Etidronate cycle consisted of 2 weeks of daily 800mg Etidronate followed by 13 weeks of no medication. Cycle was repeated once. Etidronate Treatment (n=6) Control Group (n=7)	• aBMD (hip, distal femur, proximal tibia) • Adverse event rate
Pamidronate			
Chen	2001	Daily 1000 mg elemental calcium and 0.5 µg Calcitriol for 6 days with 30 mg Pamidronate intravenous daily for 3 days (days 4, 5, and 6 of study). (n=21)	• 24-hour urine calcium and Cr • Spot urine NTx, serum calcium, phosphorus, intact PTH, 25(OH)-D, and 1,25-vitamin D.
Mechanick	2006	Daily 1000mg Calcium and 0.25 µg Calcitriol for 17 days, with a single intravenous injection of 90mg Pamidronate on day 4 (n=32)	• Serum calcium, phosphorus, albumin, urinary calcium, NTx, serum intact PTH, 25(OH)-D, and 1,25-vitamin D
Tiludronate			
Chappard	1995	Treatment for 3 months Daily 200 mg Tiludronate (n=7) Daily 400 mg Tiludronate (n=7) Placebo (n=6)	• Trabecular bone volume • Osteoid parameters • Cancellous bone mineralization rate • Osteoclast count and eroded surfaces

Appendix D: ISCD Position

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2019 ISCD OFFICIAL POSITION

Bone Mineral Density Testing in Spinal Cord Injury: 2019 ISCD Official Position

Leslie R. Morse,^{1,*} Fin Biering-Soerensen,² Laura D. Carbone,^{3,4} Tomas Cervinka,⁵
Christopher M. Cirnigliaro,⁶ Therese E. Johnston,⁷ Nan Liu,⁸ Karen L. Troy,⁹
Frances M. Weaver,^{10,11} Christopher Shuhart,¹² and Beverley C. Craven¹³

¹Department of Rehabilitation Medicine, University of Minnesota School of Medicine, Minneapolis, MN, USA; ²Clinic for Spinal Cord Injuries, Neuroscience Centre, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; ³Charlie Norwood Veterans Affairs Medical Center, Augusta, GA, USA; ⁴Department of Medicine, Medical College of Georgia, Augusta University, Augusta, GA, USA; ⁵Department of Physiotherapy and Rehabilitation, Faculty of Health and Welfare, Satakunta University of Applied Sciences, Pori, Finland; ⁶Department of Veterans Affairs Rehabilitation Research & Development Service National Center for the Medical Consequences of Spinal Cord Injury, James J. Peters Veterans Affairs Medical Center, Bronx, NY, USA; ⁷Department of Physical Therapy, Jefferson College of Rehabilitation Sciences, Thomas Jefferson University, Philadelphia, PA; ⁸Department of Rehabilitation Medicine and Osteoporosis and Metabolic Bone Disease Center, Peking University Third Hospital, Beijing, China; ⁹Department of Biomedical Engineering, Worcester Polytechnic Institute, Worcester, MA, USA; ¹⁰Center of Innovation for Complex Chronic Healthcare (CINCH), Health Services Research & Development, Department of Veterans Affairs, Hines VA Hospital, Hines, IL, USA; ¹¹Department of Public Health Sciences, Stritch School of Medicine, Loyola University, Maywood, IL, USA; ¹²Swedish Bone Health and Osteoporosis Center, Swedish Medical Group, Seattle WA, USA; and ¹³Neural Engineering and Therapeutics Team, KITE Research Institute - University Health Network, Department of Medicine, University of Toronto, Toronto, Ontario Canada

Abstract

Spinal cord injury (SCI) causes rapid osteoporosis that is most severe below the level of injury. More than half of those with motor complete SCI will experience an osteoporotic fracture at some point following their injury, with most fractures occurring at the distal femur and proximal tibia. These fractures have devastating consequences, including delayed union or nonunion, cellulitis, skin breakdown, lower extremity amputation, and premature death. Maintaining skeletal integrity and preventing fractures is imperative following SCI to fully benefit from future advances in paralysis cure research and robotic-exoskeletons, brain computer interfaces and other evolving technologies. Clinical care has been previously limited by the lack of consensus derived guidelines or standards regarding dual-energy X-ray absorptiometry-based diagnosis of osteoporosis, fracture risk prediction, or monitoring response to therapies. The International Society of Clinical Densitometry convened a task force to establish Official Positions for bone density assessment by dual-energy X-ray absorptiometry in individuals with SCI of traumatic or nontraumatic etiology. This task force conducted a series of systematic reviews to guide the development of evidence-based position statements that were reviewed by an expert panel at the 2019 Position Development Conference in Kuala Lumpur, Malaysia. The resulting the International Society of Clinical Densitometry Official Positions are intended to inform clinical care and guide the diagnosis of osteoporosis as well as fracture risk management of osteoporosis following SCI.

Key Words: Dual-energy X-ray absorptiometry; guidelines; official positions; spinal cord injury.

Background

The spinal cord injury (SCI) task force was convened to address 4 questions developed by the International Society for Clinical Densitometry (ISCD) related to the clinical utility of bone density assessment by dual-energy X-ray absorptiometry (DXA) in individuals with SCI. Five SCI task force working groups composed of 2-4 task force member each were organized to conduct literature searches for each of the 4 questions. An Information Specialist (MP) developed database search strategies for each of the searches following the PICO (Patient/ Problem, Intervention, Comparison/Control, Outcome) framework and utilizing subject headings as appropriate for each database and free text terms relevant to the topical concepts. The 7 databases searched from inception to November 19, 2018, included: CINAHL, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Embase, Emcare, Medline, and PubMed (excluding Medline records). The results were limited to English language and human materials. The search strategy for each question can be found in Appendix A. After eliminating duplicates, citations were imported to Covidence, a web-based systematic review tool (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia; Available at www.covidence.org), for all team members to easily access. For each search, one task force member reviewed all titles and abstracts. Full text review and reasons for exclusion were assessed independently by 2 reviewers and conflicts were addressed during a discussion between the 2 reviewers. Data were extracted independently and then compared. Evidence-based position statements were developed to address each question and are presented in the following section. Tables summarizing each literature search can be found in the online appendix.

Clinical Considerations

While the bulk of evidence regarding bone health and SCI is derived from studies restricted to traumatic SCI, we recommend that the following position statements be applied clinically to individuals with either traumatic or atraumatic SCI. These position statements do not apply to other disorders of the spine that do not result in permanent loss of sensory or motor function below the level of the injury. Additionally, there are practical issues to be considered in the clinical care of individuals with SCI. In all cases, DXA scans should be performed in a room with an adequate turning radius for a manual

or power wheelchair and be equipped with a lift. DXA measures of regions of interest containing technical artifacts, such as hardware, deformity, heterotopic ossification, contracture, or movement (spasticity) or leg bag artifacts which prevent optimal positioning for scan acquisition or limit the accuracy of the analysis should not be used for diagnosis, fracture risk assessment, or monitoring response to therapy.

Key Questions

Question 1: What are the indications for initial DXA in individuals with spinal cord injury?

Question 2: Can bone densitometry by DXA be used to diagnose osteoporosis, assess fracture risk, or monitor response to therapy in individuals with spinal cord injury?

Question 3: How should DXA be used to monitor osteoporosis therapy (drug, nutraceuticals, rehabilitation interventions) in individuals with SCI?

Question 4: Are there DXA based criteria that are absolute or relative contra-indication to exercise-based therapy?

ISCD Official Position Statement

- All adults with spinal cord injury resulting in permanent motor or sensory dysfunction should have a DXA scan of the total hip, proximal tibia, and distal femur as soon as medically stable.

Grade: Fair, B, W

Rationale

In the healthy non-SCI population, the ISCD recommends DXA testing regardless of clinical risk factors in all postmenopausal women age 65 and older and men older than 70 (1). In view of the preponderance of low bone mass and/or osteoporosis and the substantially higher rates of loss of BMD in the SCI population compared with the healthy population without a SCI of a similar age and sex, a SCI in and of itself is an indication for an initial and serial DXA testing. Although there are some differences in extent of bone loss by age, race, time since injury, ambulatory status, sex, and in particular, level and completeness of injury, all persons with a SCI, regardless of these factors, should have a baseline DXA.

Discussion

Multiple studies consistently report that areal BMD measurements by DXA in persons with a traumatic SCI at the hip (2-11), distal femur (2,7,9,12-15), and proximal tibia (4,7,16-18), but not the lumbar spine (2,3,6,9,19,20), are substantially lower than that of the general population of similar age and gender. The majority of individuals with SCI have osteoporosis or low bone mass (4,8,21). Further, impressive and rapid declines in areal BMD occur very early following SCI, with losses reported at the hip (22-25), proximal tibia (22,26), and distal femur (22,24). In persons with an acute SCI of 1 yr or less, reported losses of BMD by DXA within 12 mo at the femoral neck and total hip range from 4.5% to 20% and 3.0% to 21.1%, respectively (23,27-29). In one study, normal mean baseline Z-scores at the total hip and femoral neck had declined at both 6 and 12 mo to a level below normal for age ($Z \leq -2.0$) (30). In contrast, Maimoun et al (31), did not find significant differences in BMD at the proximal femur, spine or radius in SCI vs non-SCI controls, but the sample size was small ($n = 7$). On average, though, it has been suggested that areal BMD losses at the hip approximate 2% per month in acute motor complete SCI (27).

In persons with a SCI of a more chronic duration (greater than 1 yr postinjury), loss of BMD continues at the hip, (32-35), proximal tibia (13,34), and distal femur (13) with ongoing continued losses documented in one study over a 5 yr span at the femur and tibia (13). Low BMD at multiple skeletal sites has also been reported in those with nontraumatic disorders (11,36,37). These losses of BMD in SCI are much greater than the average rate of loss in healthy postmenopausal women or in age-related bone loss. In the general population, BMD losses by DXA average 1% to 2% per year with higher rates at 2% to 4% per year, in the first 5 to 10 yr after menopause (38) and approximate 0.5% per year with aging (39), although there is variation in rates of bone loss within individuals and by sites measured. Current recommendations for DXA testing in the healthy non-SCI population are for DXAs to be measured in all postmenopausal women age 65 and older, and men older than age 70. Thus, since BMD is lower and rates of bone loss by areal DXA are substantially higher in persons with a SCI, compared to the general population, we suggest that having a SCI is in itself an indication for an initial DXA scan. Further,

since rates of bone loss are fastest acutely following injury or disease, it is suggested that DXA testing should be done as soon as possible following injury.

There are several reports regarding the association of age, race, sex, medication use, and prevalent fracture with areal BMD by DXA. We found ten articles that examined the association between age and areal BMD by DXA in persons with a SCI (13,16,40-46). Studies that reported on age had mixed results. Four studies found no relationship (13,43,44). In 2 studies (10,16) Garland et al found an inverse relationship between age and hip BMD. Lazo et al (42) also found an inverse relationship with younger SCI patients (mean age of 45) more likely to have normal BMD while both those with osteopenia and osteoporosis were significantly older. Two studies found sex-specific age results. Kiratli et al (40) reported an age-related decrement in BMD that was greater for women than men. Javidan et al (41) found a negative relationship between age and femoral neck BMD Z-scores for males only.

Regarding the association of race with BMD by areal DXA in SCI, few studies report on the racial breakdown of their study cohorts. Only one study, a cross sectional analysis of 247 Veterans with SCI (47) specifically examined the association of race with BMD in SCI and reported that blacks with SCI were more likely to have normal BMD than nonblacks with SCI. Similarly, few studies have included women in their samples, and even when they do, the number is small. Only 2 studies specifically examined sex differences in BMD by DXA in persons with a SCI. In both studies there appeared to be an interaction of sex with other factors (40,41).

Most studies examining BMD and level of injury compared individuals with paraplegia vs tetraplegia. Ten of 11 studies did not find a relation between level of injury and bone loss (44,45,48-53). These studies often did not consider ambulatory status or completeness of injury, in addition to level of injury. Wang et al (54), however, did report lower BMD of the lumbar spine for individuals with T6 or higher-level injuries.

Twelve (16,43,45,47,51,55-58) studies included severity of SCI, predominately defined as complete or incomplete injuries. Five found a relationship between BMD change and severity with Abderhalden

(47) reporting less BMD loss for incomplete injuries, and Pearson et al (1997) (57) finding less BMD loss for individuals who were ambulatory. More recently, Morse et al (2016) (59) reported bone loss was significantly greater in participants with chronic SCI who used a wheelchair compared to walkers. Kostovski et al (56) found lower femur BMD to be related to greater impairment based on the American Spinal Injury Association (ASIA) Impairment Scale (AIS) (60). Sabo et al (49) reported significantly lower BMD in the lumbar spine of persons with complete injuries compared to incomplete injuries. Liu et al (58) found a positive trend between greater severity (defined as level by completeness of injury) and BMD loss and Garland et al (61) found that the extent of neurologic deficit was related to BMD loss at the hip and knee.

Studies frequently examined the relationship between BMD and duration of injury. Less than half (7 of 17) did not find a relationship between duration of SCI and BMD (13,34,42,44,48,54,58). Ten studies reported an inverse relationship. Lazo et al (42) found a relationship between duration of injury and greater incidence of osteoporosis (42). Zehnder (2004) (62) reported increased duration of injury as positively related to fracture incidence and Hammond (55) found increased duration of injury to be associated with osteoporosis. Bauman (63) found duration of injury to be significantly inversely related to BMD of the spine. Gaspar (9) found an inverse relationship between femur BMD and duration, and Garland, (13) found an inverse relationship between duration of injury and hip BMD. Paker (43) also reported lower hip BMD with greater duration of SCI. Schnitzer (50) found greater BMD loss at the hip and femoral neck in chronic vs acute SCI cases and Szollar (52) reported gradual decline in BMD of the femoral regions over time. Finally, Liu (58) found a correlation between injury duration and lower BMD of the femoral neck.

Most studies that examined factors related to declining bone mass in SCI excluded individuals on any medications that can affect bone metabolism (e.g., hormones, steroid, supplements, and osteoporosis medications). Chain (64) found a positive relationship between habitual calcium intake and spine BMD while Hammond (55) did not find a relationship between calcium and Vitamin D with osteoporosis risk. Few studies examined the association of prevalent

fracture on risk of osteoporosis in SCI. Hammond (55) found no relationship between prevalent fractures and osteoporosis risk while Lala (2014) (65) reported a relationship between prior fracture and decreased BMD at the distal and proximal femur and total hip.

In summary, areal BMD and rates of loss of areal BMD by DXA in persons with SCI do appear to vary by a number of clinical characteristics. In particular, the majority of the literature suggests that loss of BMD is greatest acutely following injury and in those with complete injuries. While bone loss occurs in all cases after injury, it is most extreme following motor complete SCI. Because SCI itself is such a profound risk factor for low BMD and loss of BMD, irrespective of other clinical characteristics, an initial DXA should be done in all persons with a SCI.

Additional Questions for Future Research

Suggested areas for future research include further studies of losses of BMD in individuals with SCI, in particular, nontraumatic disorders, and women using ISCD recommendations to calculate root mean square coefficient of variation (RMS-CV) at sites of BMD measurements in SCI-populations. Further studies are needed to characterize sex and racial differences and the impact of medications and fracture history on BMD and regional decline in BMD among individuals with SCI. Additionally, opportunistic assessment of BMD based on CT scans obtained during management of acute trauma may also improve bone health assessment. Additional work is needed to address this.

ISCD Official Position

- In adults with SCI, total hip, distal femur and proximal tibia bone density should be used to diagnose osteoporosis, predict lower extremity fracture risk and monitor response to therapy where normative data are available.

Grade: Fair, B, W

Rationale

After SCI, bone loss occurs rapidly and continuously in the lower extremities (25). This is linked to a high risk of fracture in the legs, and particularly around the knees (61,65). Fracture risk is strongly associated with and can be predicted by low bone mass for a given age or osteoporosis diagnosis based on T- or Z-score

threshold criteria. Similarly, individuals with SCI and with prevalent fragility fractures have significantly lower bone density compared to those with SCI who do not have a history of prevalent fracture. The gradient for fracture risk based on T-score is much greater than the typical T-score gradient in post-menopausal or age-related osteoporosis.

Discussion

Bone Loss After SCI Occurs in the Lower Extremities

Generally, no change in BMD is seen in the lumbar spine after SCI either in longitudinal studies or in comparison with able-bodied individuals (7,13,31,45,66,70), but degenerative changes within the posterior elements, heterotopic ossification, or hardware may falsely increase BMD in the spine (63,71). No significant changes in BMD after SCI were found in the proximal and distal forearm (radius and ulna) (15), radius (64,67), forearm (66), or arm (45,72,73). However at the same time individuals with tetraplegia may have lower BMD than those with paraplegia (25,74,75), and these sites may even have higher values than normal (31,33,76), not least if performing upper extremity activities (e.g., wheelchair basketball) (68). The BMD loss is greater around the knee than in the hip-region after SCI (2,10,13,22,25,40,57,66,77), and the loss is greater in individuals with motor complete lesions (25,29,49). Studies comparing the BMD loss in the distal femur and the proximal tibia after SCI show a greater loss at the distal femur (57,78) as well as in the proximal tibia (13,22,29), often without major differences between the sites.

Reliable Protocols Have Been Established for Distal Femur and Proximal Tibia

There are no standardized protocols developed by DXA machine manufacturers to measure BMD at the distal femur or proximal tibia. However, several groups have developed or adopted protocols for measurement at these sites and report percent coefficient of variation (%CV) data for distal femur and proximal tibia. Several protocols report the use of knee positioning devices to improve repeatability. These protocols utilize one of 3 general acquisition approaches: lumbar spine software (7,65), distal forearm software, or custom research software (79). Most measure the entire width of the tibia or femur within the analysis region of interest (ROI), although there are differences in how specific ROIs are identified. Protocols that

utilize sub regions from total body DXA are not recommended due to poor repeatability, sensitivity to patient positioning, and an imaging resolution that is not sensitive to small differences in BMD. Several groups have reported protocol validation/precision data, but only one (80) compares values to another measurement technique (quantitative computed tomography) to evaluate accuracy.

We recommend that standard methodology and normative data be adopted by the field at the distal femur and proximal tibia sites. In the absence software from the manufacturers for to determine BMD at these regions clinically, the Toronto Rehab Protocol (65) for determination of bone density at the knee region is a feasible protocol that can be widely adopted and implemented. This protocol utilizes lumbar spine software and can be used with a T- or Z-score calculator for the distal femur and proximal tibia that can be accessed at the following link: <https://kite-uhn.com/clinical/tools/knee-dxa-protocol>. When possible, precision studies for the determination of least significant change ($LSC = 2.77 \times CV$) should be calculated using individuals with SCI, since suboptimal positioning and heterotopic ossification are common in this population and are expected to reduce precision.

BMD and Fracture Risk in SCI

We found 5 articles that addressed risk of prevalent fracture based on BMD (42,61,62,65,81) and one article that addressed risk of incident fracture based on bone density after SCI (47). There is agreement in the literature that lower extremity bone density is lower in individuals with SCI that have a prevalent fragility fracture. Fragility fractures are most common at the distal femur and proximal tibia after SCI (82,83). Initial reports focused on bone density the hip, a skeletal site easily obtained by standard clinical DXA scanning protocols. In a cross-sectional analysis of 41 men with SCI, Lazo et al.(42) reported that those with a prevalent fragility fracture had 37% lower bone density at the femoral neck than those with no fracture (mean BMD = 0.504 g/cm² vs 0.786 g/cm², $p < 0.001$). The risk of having had a fracture increased 2.2 times for each 0.1 g/cm² of decline in bone density at the femoral neck. Garland et al. (61) were among the first to report changes in bone density at the knee after SCI. Using a technique that measured regional knee bone density and included both distal femur and proximal

tibia combined, the authors reported a 16% reduction in knee bone density in individuals with a fracture history compared to those with no fracture history (mean = 0.6287 g/cm² vs mean = 0.5279 g/cm²). In agreement with these findings, a more recent study by Tan and colleagues found that non-ambulatory men with SCI and prevalent fractures had significantly lower bone density at both traditional and SCI-specific skeletal sites (81). The authors found that bone density was 24% 25% lower at the total hip and femoral neck and 43% 44% lower at the distal femur and proximal tibia in the fracture group compared to the no fracture group. The larger differences in distal femur/proximal tibia bone densities in the Tan paper are unclear but may be attributed to differences in participant demographics or scanning methodology. Consistent with these findings, additional studies have found that T- and Z-scores are significantly lower at the femoral neck, distal femur, and proximal tibia in individuals with prevalent fractures (62). Furthermore, in one of the first reports of incident fracture in persons with SCI, Abderhalden et al (47), performed a retrospective study of veterans with SCI stratifying risk for fracture by T-score into normal, osteopenia, and osteoporosis groups. The authors reported that hip T-score was significantly lower in veterans with incident fracture compared to those without fracture (2.71 vs 2.24, p = 0.05). In another study by Lala (65), significantly lower mean BMD values were observed in those with history of fracture (n = 6) compared to those with no fracture (n = 21). After adjusting for injury completeness, the authors found the risk of having had a fracture increased 4.9 times for each standard deviation decrease in bone density at the distal femur and 6.1 times for each standard deviation decrease in bone density at the proximal tibia.

Additional Questions for Future Research

Manufacturer-established standard protocols for bone density measurement at the knee as well as a large, SCI- specific normative datasets are needed. Bone density measurement at the calcaneus may be useful for osteoporosis diagnosis in individuals with SCI (26,84,85). This site demonstrates post-SCI bone loss and is easily accessible with peripheral devices or alternate measurement methods such as quantitative ultrasound (86). However, further research is needed to establish the validity and clinical utility of bone density measures at this site in people with SCI.

While BMD is an important fracture risk predictor, several analyses have identified the importance of additional lower-extremity SCI-specific fracture risk factors. In addition to the BMD, these non-BMD clinical risk factors need to be considered when evaluating fracture risk among individuals with SCI: history of fragility fracture (20), family history of fragility fracture (20), body mass index <19 (18), duration of injury 10 yr (21), female sex (21,22), age at injury < 16 yr (23), motor complete injury (24), paraplegia (25), alcohol use > 5 servings per day (26) and use of specific medications including opioid analgesia (27,38), benzodiazepines (28), or unfractionated heparin (27,28). Additional work is needed to fully quantify risk of incident fracture based on bone density at both traditional (femoral neck, total hip) and SCI-specific skeletal sites (distal femur, proximal tibia) and based on demographic characteristics including race, sex, age, ambulatory status, injury level and severity, and time since injury.

ISCD Official Position

- Serial DXA assessment of treatment effectiveness among individuals with SCI should include evaluation at the total hip, distal femur, and proximal tibia, following a minimum of 12 mo of therapy at 1- to 2-yr intervals. Segmental analysis of total hip, distal femur and proximal tibia subregions from a whole-body scan should not be used for monitoring treatment.

Grade Fair, B, W

Rationale

Serial BMD testing can be used to identify fracture risk and monitor response to therapy, regardless of the nature of the intervention or intervention(s) such as drug, nutraceutical, exercise or rehabilitation interventions alone or in combination. Studies demonstrate the ability to detect significant changes in bone density in response to therapies after SCI. There is level I evidence (Alendronate, vitamin D₂, and combination therapy with teriparatide/ vibration and standard care) for sustained increments in hip, distal femur or proximal tibia BMD from baseline in adults with chronic SCI and established low bone mass. Evaluating increments in lumbar spine BMD, although a clinical standard in the field of densitometry, is considered less relevant in the field of SCI, as BMD

values at this anatomic site often fall within the normal range at baseline, the values are often inaccurate due to posterior element artifacts, regional hardware, or an insufficient number of contiguous vertebrae for assessment among those with conus or cauda equine lesions.

Discussion

For the development of this position statement, we reviewed twenty studies evaluating therapeutic interventions that enrolled individuals who were at least 1-yr post-injury. The following interventions with DXA as an outcome for treatment of low bone mass were reviewed: (A) pharmacological interventions with alendronate (87), denosumab (88), zoledronate (33); (B) nutraceutical intervention with vitamin D₂ (89); (C) exercise interventions: Functional Electrical Stimulation (FES)-cycling (3,17,70,90-92), FES-walking (93), Body Weight Support Treadmill Training (BWSTT) (94), Neuromuscular Electrical Stimulation (NMES) (95), passive standing (96), upper extremity vibration (97) and, (D) intervention combinations with: (1) Robotic treadmill training with partial body weight support; (2) teriparatide with lower limb vibration (98), (3) whole body and passive standing in a standing frame (99).

A majority of studies evaluated BMD of the lumbar spine (n = 11/20) and hip (n = 12/20), with 5 exercise interventions evaluating distal femur and proximal tibia BMD at 6 mo or 1 yr. Looking across all the interventions at serial DXA testing intervals: 2 studies had 6 mo (92,95) and 2 had 12 mo (17,88) BMD outcomes, and 3 studies had both 6 and 12 mo DXA outcomes (30,70,98), of which the changes in BMD were not significant at 6 mo for 2 (30,98) of the 3 aforementioned studies. In addition, Mohr (17) measured serial DXA values at 18 mo (17), Bauman at 18 and 24 mo (89), and Edwards at 24 mo (98).

To date, there are few studies with Level I evidence (i.e., evidence obtained from at least one properly designed randomized controlled trial) of efficacy for therapeutic efficacy of interventions for individuals chronic SCI with established low bone mass. Importantly, no studies evaluated fracture risk reduction as an outcome. The following Level 1 evidence statements, specifying the intervention type and duration, and the time period between intervention initiation and conduct of serial DXA scans, were used to inform the aforementioned position

statement. For pharmacological interventions, 6 mo of alendronate 10 mg once daily with 500 mg of calcium twice daily maintains BMD of the total body, upper extremity and lower extremity in adults with spinal cord impairment (87). In contrast, IV zoledronate 4 mg annually was ineffective in increasing BMD of the hip, femoral neck, and 1/3 distal radius (33) among adults with SCI. For nutraceuticals, 12 mo of therapy with Vitamin D₂ increased BMD of the lower extremity (89). For exercise interventions, 4 mo of surface FES-walking for 45 min thrice weekly did not increase lumbar spine, hip, distal femur or proximal tibia BMD at 1 yr (93). Furthermore, 6 mo of high cadence (50 rpm) FES-cycling and low cadence (20 rpm) FES-cycling does not increase lateral distal femur BMD (90) when repeated 3 times weekly for 1 h. In general, there is a paucity of studies evaluating the longitudinal (more than 6 mo) benefits of exercise interventions; increasing the risk of a type II error when BMD change is the outcome of interest. For combination therapy, 12 mo of teriparatide 20 mcg/d plus vibration 10 min/d versus placebo and sham vibration 10 min/day with calcium 1000 mg/day and vitamin D 1000 IU/d increases lumbar spine and total hip BMD and maintains femoral neck BMD (98) in adults with paraplegia and tetraplegia AIS A-D impairment.

Based on these findings, either pharmacological or exercised-based therapeutic intervention should be considered among individuals with SCI, regardless of injury etiology, who meet diagnostic criteria for osteoporosis, or who have any total hip (femoral neck), distal femur, or proximal tibia region BMD Z-score of ≤ 2.0 (93), or a prior lumbar spine compression fracture or lower extremity fragility fracture (hip, distal femur or proximal tibia). A distal femur BMD value ≥ 0.561 g/cm² (65) has also been proposed as an indication for treatment. However, this value was determined on one manufacturer's machine (Hologic 4500A) and using one protocol to determine BMD (Toronto Rehab Protocol) and has not been validated on other machine models or using other BMD protocols. Serial DXA scans are used to monitor adult men and women with SCI and low BMD of the hip, distal femur and/or proximal tibia regions requiring therapy to: maintain BMD, prevent fracture, or evaluate the effectiveness or nonresponse to therapy with a drug, nutraceutical, or exercise interventions, alone, or in combination. The time interval between serial scans, on the same densitometer, should extend

from therapy initiation to an interval of time beyond which the anticipated maintenance or increments in hip, distal femur and proximal tibia BMD, in response to the therapy, meets, or exceeds the LSC of the DXA system. Once the therapeutic effectiveness of an intervention is established, the time interval between serial scans may be extended. Throughout the available published literature there was inadequate reporting of the densitometer LSC at all of the anatomic sites evaluated, with the exception of 4 studies: 2 intervention studies (70,93), 1 observational study (11), and 1 cross-sectional study (64).

In the context of SCI, treatment effectiveness should be defined as stability, or an increase, in absolute BMD (g/cm^2) at the anatomic site, which is equal to, or greater than, the LSC for the scanner or facility at that anatomic site (lumbar spine, total hip, distal femur, or proximal tibia). Clinicians and researchers are encouraged to look at absolute changes in BMD (g/cm^2) before making decisions regarding therapeutic effectiveness among individuals with chronic SCI, as large relative percent changes from the time of initiating therapy are observed, with small absolute changes in BMD values (g/cm^2). Few studies reported increments in BMD (relative or absolute): 2 at the lumbar spine (88,98), 3 at the total hip (17,70,88), 2 at the distal femur (70,95), 3 at the proximal tibia (17,70,95), and 2 of the leg sub regions of total body scans (92,100). Bauman and colleagues (89) reported $0.021 \text{ g}/\text{cm}^2$ change in lower extremity BMD after 12 mo of Vitamin D2 intervention and this increase remained stable over an additional 12 mo. Belanger et al (95) reported $0.082 \text{ g}/\text{cm}^2$ and $0.052 \text{ g}/\text{cm}^2$ change in distal femur and proximal tibia BMD after 6 mo of NMES intervention, respectively. Chen et al (70) reported $0.06 \text{ g}/\text{cm}^2$ change in femoral neck BMD, and $0.08 \text{ g}/\text{cm}^2$ and $0.072 \text{ g}/\text{cm}^2$ change in distal femur and proximal tibia after 6 mo of FES-cycling, respectively. Mohr et al (17) showed $0.02 \text{ g}/\text{cm}$ change in femoral neck BMD and $0.05 \text{ g}/\text{cm}$ change in proximal tibia BMD after 12 mo of FES-cycling.

Additional Questions for Future Research

Additional work is needed to identify novel therapeutic interventions, both rehabilitation and pharmacological, to augment bone mass and reduce fracture risk in SCI. A better understanding of repeat performance characteristics of SCI-specific regions of interest is needed, including deter- mining least significant

change and root mean square coefficient of variation at each site. Additional work is also needed to refine monitoring recommendations based on clinical characteristics, including level of injury and motor completeness.

ISCD Official Position

- There is no established threshold BMD value below which weight-bearing activities are absolutely contra- indicated. BMD and clinical risk factors should be used to assess fracture risk prior to engaging in weight-bearing activities.

Grade: Poor, C, W

Rationale

There is great interest in using DXA-derived bone density values to determine safety for participation in weight-bearing therapies, both clinically and from a research perspective, after SCI. Overall, there is a lack of evidence to support a T-score cutoff as a contraindication for safe participation in rehabilitation interventions. While few fractures have occurred, most of these have involved upright weight bearing gait training activities, suggesting increased risk with these interventions. However, other studies using these gait training modalities reported no fractures. We recommend determining BMD for all individuals with SCI with additional screen required for T-score < 2.0 to assess fracture risk prior to initiating weight-bearing therapies.

Discussion

Few studies report fractures occurring during rehabilitation therapies. Of the 15 studies that report fractures occurring, fractures in 8 of these studies were directly related to the study intervention, 5 studies reported unrelated fractures, (8,101-104) and 2 reported fractures of unclear etiology (105-107). Five fractures reportedly occurred during upright weight bearing gait training delivered via treadmill training and/or robotics with or without electrical stimulation (107-110). The remaining 3 fractures occurred during Functional Electrical Stimulation (FES)-cycling (111), maximal exercise using electrical stimulation,(112) and unspecified exercise (113). Of these 15 studies reporting participants with fractures, only one study used DXA scans pre-intervention to assess BMD and to determine potential safety, and only 5 reported excluding participants with prior

fractures (8,103,108,109,111,114). Fourteen studies (18,36,37,93,95,115-122) reported that no fractures occurred during intervention with 2 studies (1 gait training (122) and 1 FES cycling (121) excluding participants with T-scores <-2.5, and 5 studies excluding those with prior fractures (18,36,94,95,117,121). One additional study (95) used DXA to only note the presence of a fracture for study exclusion purposes. Fifty-eight study authors did not report presence or absence of fractures. Of these studies, 9 used DXA to exclude individuals with low T-score cutoffs ranging from 2.5 to 4.0 (123-130), or BMD of <0.6 0.7 g/cm (131). Seventeen studies excluded participants based on prior fractures (11,22,24,70,90,92,126,127,131,138). The remaining 35 studies reported no T-score or fracture-related exclusion criteria (3,17,28,45,55,64,97,139-166).

Few studies included DXA criteria or prior fractures as exclusions for rehabilitation therapies, and those using DXA had a large range for T-scores cutoffs (< 2.5 to 4.0). Thirty-six studies reported using other non-DXA or fracture related exclusion criteria that focused on the presence of specific medical conditions that could impact bone, range of motion deficits, and postfracture healing, and surgical intervention. Based on the lack of a T-score cutoff, these factors are important to consider when determining the safety of rehabilitation therapies for an individual with SCI. Thus, we recommend screening all patients with SCI before implementing rehabilitation interventions. This screening must include DXA of the hip (total, femoral neck), distal femur and proximal tibia, ideally within 30 d post-SCI. If the T-score of these areas is < 2.0, further screening is required to identify prior fractures, range of motion limitations impacting performance of the specific rehabilitation therapy, and any medical conditions that may negatively impact bone. Screening for occult foot and ankle fractures prior to initiating rehabilitation interventions is also strongly encouraged. These combined risks must be evaluated by the rehabilitation team, which must then discuss the potential benefits and risks with the individual participant.

Additional Questions for Future Research

Possible underreporting of fractures during rehabilitation interventions is a concern in the current literature. Thirty-eight studies did not state whether a fracture occurred or not. Thus, it is not known if

fractures occurred in these studies and were not reported. A mandate for reporting the presence or absence of fractures is needed for all studies implementing rehabilitation interventions in individuals with SCI. All future studies with DXA derived BMD outcomes should report means and ranges of both bone density and T-scores as well as information about other conditions following the guidelines in this position statement. This standardization is needed to allow determination of T-score cutoffs and other criteria for safety.

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Supplementary materials

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Appendix E: Risk of Bias (ROB) Tables

SECTION 5.0 - Calcium and Vitamin D3: Diet or Supplements

Table 5.1. ROB assessment for studies used to inform recommendations pertaining to nutritional interventions for bone health.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Group similarities at baseline	Specified eligibility criteria	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Selective reporting (reporting bias)	Incomplete outcome data (attrition bias)	Analysis according to randomization	Non-biased selection	Incomplete outcome data (attrition bias)	Pre-specified/defined outcomes	Adequate description of methodology	Non-biased and adequate methodology	Statistical analysis of potential confounds	Adequate duration of follow up
Bauman 2005	?	?	+	+	+	+	?	+	+	?	+	+	+	+	+	+
Hatefi 2018	?	?	+	+	+	+	?	+	+	?	+	+	+	+	+	+
Moran de Brito 2005	?	?	+	+	?	?	?	+	+	?	+	+	+	+	+	?
Zehnder 2004b	+	+	+	+	+	+	?	?	+	+	+	+	+	+	?	?

High
 Unclear
 Low

SECTION 6.0 – REHABILITATION THERAPY

Table 6.1. Risk of bias summary of randomized controlled trials pertaining to the use of standing/walking to prevent low bone mass or osteoporosis.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Group similarities at baseline	Specified eligibility criteria	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Selective reporting (reporting bias)	Incomplete outcome data (attrition bias)	Analysis according to randomization
De Bruin 1999	?	?	+	+	?	?	+	+	?

High
 Unclear
 Low

Table 6.2. Risk of bias summary of observational studies pertaining to the use of standing/walking to prevent low bone mass or osteoporosis

	Non-biased selection	Incomplete outcome data (attrition bias)	Pre-specified/defined outcomes	Adequate description of methodology	Non-biased and adequate methodology	Statistical analysis of potential confounds	Adequate duration of follow-up
Alekna 2008	?	+	+	+	+	+	+
Dudley-Javoroski 2012	+	+	+	+	+	?	?
Eser 2003	+	+	+	+	+	+	?

High
 Unclear
 Low

Table 6.3. Risk of bias summary of randomized control trials pertaining to use of treadmill training to prevent low bone mass or osteoporosis

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Group similarities at baseline	Specified eligibility criteria	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Selective reporting (reporting bias)	Incomplete outcome data (attrition bias)	Analysis according to randomization
De Bruin 1999	?	?	+	+	?	+	+	+	?
	High	Unclear	Low	Low	Unclear	Low	Low	Low	Unclear

Table 6.4. Risk of bias summary of observational studies pertaining to use of treadmill training to prevent low bone mass or osteoporosis

	Non-biased selection	Incomplete outcome data (attrition bias)	Pre-specified/defined outcomes	Adequate description of methodology	Non-biased and adequate methodology	Statistical analysis of potential confounds	Adequate duration of follow-up
Giangregorio 2005	+	+	+	+	+	?	+
	Low	Low	Low	Low	Low	Unclear	Low

Table 6.5. Risk of bias summary of observational studies pertaining to use of functional electrical stimulation (FES) to prevent low bone mass or osteoporosis

	Non-biased selection	Incomplete outcome data (attrition bias)	Pre-specified/defined outcomes	Adequate description of methodology	Non-biased and adequate methodology	Statistical analysis of potential confounds	Adequate duration of follow-up
Eser 2003	+	+	+	+	+	+	+
Lai 2010	?	+	+	+	+	?	+
Lambach 2018	?	+	+	+	+	+	+
	Unclear	Low	Low	Low	Low	Unclear	Low

Table 6.6. Risk of bias summary of randomized control trials pertaining to use of neuromuscular electrical stimulation (NMES) to prevent low bone mass or osteoporosis

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Group similarities at baseline	Specified eligibility criteria	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Selective reporting (reporting bias)	Incomplete outcome data (attrition bias)	Analysis according to randomization
Arija-Blazquez 2014	+	?	+	+	+	+	?	+	?
Groah 2010	+	?	+	+	+	+	?	+	?
	Low	Unclear	Low	Low	Low	Low	Unclear	Low	Unclear

Table 6.7. Risk of bias summary of observational studies pertaining to use of neuromuscular electrical stimulation (NMES) to prevent low bone mass or osteoporosis

	Non-biased selection	Incomplete outcome data (attrition bias)	Pre-specified/defined outcomes	Adequate description of methodology	Non-biased and adequate methodology	Statistical analysis of potential confounds	Adequate duration of follow-up
Clark 2007	High	High	Low	Low	High	Low	Low
Dudley-Javoroski & Shields 2008a	Unclear	Low	Low	Low	High	High	Low
Dudley-Javoroski 2012	Low	Low	Low	Low	High	Unclear	Unclear
Shields 2006a	Low	High	Low	Low	High	Low	Low
Shields 2006b	Unclear	High	Low	Low	High	Low	Low

High

Unclear

Low

Table 6.9. Risk of bias summary of observational studies pertaining to overground walking to treat low bone mass or osteoporosis

	Non-biased selection	Incomplete outcome data (attrition bias)	Pre-specified/defined outcomes	Adequate description of methodology	Non-biased and adequate methodology	Statistical analysis of potential confounds	Adequate duration of follow-up
Ogilvie 1993	Unclear	Low	Low	Low	High	High	Low
Thoumie 1995	Unclear	Low	Low	High	Unclear	High	Low

High

Unclear

Low

Table 6.8. Risk of bias summary of observational studies pertaining to use of passive standing to treat low bone mass or osteoporosis

	Non-biased selection	Incomplete outcome data (attrition bias)	Pre-specified/defined outcomes	Adequate description of methodology	Non-biased and adequate methodology	Statistical analysis of potential confounds	Adequate duration of follow-up
Goktepe 2008	Unclear	Low	Low	Low	Low	Low	

High

Unclear

Low

Table 6.10. Risk of bias summary of observational studies pertaining to use of treadmill training to treat low bone mass or osteoporosis

	Non-biased selection	Incomplete outcome data (attrition bias)	Pre-specified/defined outcomes	Adequate description of methodology	Non-biased and adequate methodology	Statistical analysis of potential confounds	Adequate duration of follow-up
Giangregorio 2006	Low	Low	Low	Low	High	High	Low

High

Unclear

Low

Table 6.11. Risk of bias summary of observational studies pertaining to the use of NMES to treat low bone mass or osteoporosis.

	Non-biased selection	Incomplete outcome data (attrition bias)	Pre-specified/defined outcomes	Adequate description of methodology	Non-biased and adequate methodology	Statistical analysis of potential confounds	Adequate duration of follow-up
Belanger 2000	+	+	+	+	+	+	+
Shields 2007	?	-	+	+	+	+	+

- High ? Unclear + Low

Table 6.12. Risk of bias summary of randomized controlled trials pertaining to use of FES to treat low bone mass or osteoporosis

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Group similarities at baseline	Specified eligibility criteria	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Selective reporting (reporting bias)	Incomplete outcome data (attrition bias)	Analysis according to randomization
Craven 2017	+	+	+	+	-	+	?	-	+
Johnston 2016	+	+	+	+	?	?	+	+	?
Morse 2019	?	?	+	+	?	?	-	-	?

- High ? Unclear + Low

Table 6.13. Risk of bias summary of observational studies pertaining to use of FES to treat low bone mass or osteoporosis.

	Non-biased selection	Incomplete outcome data (attrition bias)	Pre-specified/defined outcomes	Adequate description of methodology	Non-biased and adequate methodology	Statistical analysis of potential confounds	Adequate duration of follow-up
Ashe 2010	+	+	+	+	+	+	+
BeDell 1996	-	+	+	+	+	+	+
Bloomfield 1996	+	-	+	+	+	+	+
Carvalho 2006	?	+	+	+	-	-	+
Chen 2005	+	+	+	+	+	+	+
Dudley-Javoroski 2012	+	+	+	+	-	?	?
Frotzler 2008	+	+	+	+	+	+	+
Frotzler 2009	-	+	+	+	+	+	+
Hangartner 1994	-	+	+	+	+	+	+
Leeds 1990	-	+	+	+	+	+	+
Mohr 1997	+	+	+	+	+	+	+
Needham-Shropshire 1997	?	+	+	-	-	-	+
Pacy 1988	-	+	+	+	+	+	+

- High ? Unclear + Low

SECTION 7.0 – drug THERAPY

Table 7.1. Risk of bias summary of a randomized controlled trial in which alendronate was used to prevent bone loss in a cohort of individuals with acute spinal cord injury.

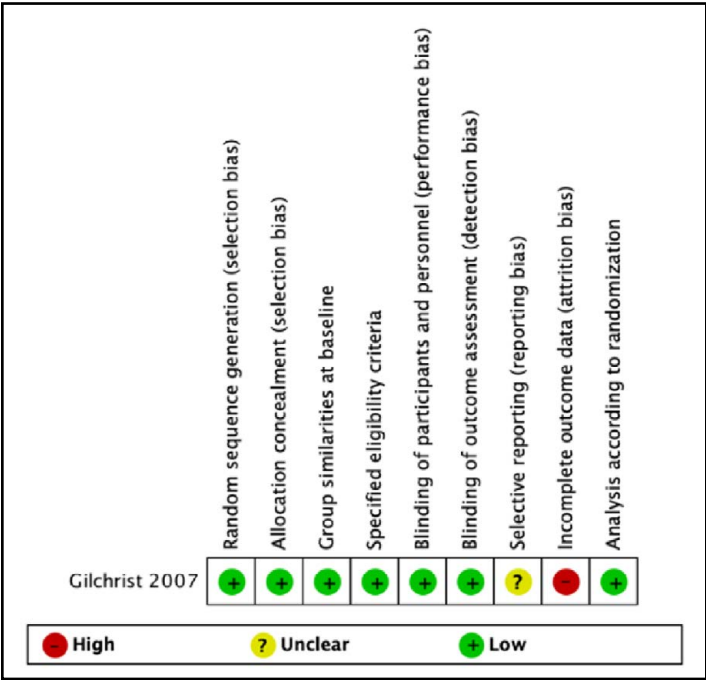


Table 7.2. Risk of bias summary for a non-randomized control trial which pamidronate was used to prevent bone loss in a cohort of individuals with acute spinal cord injury.

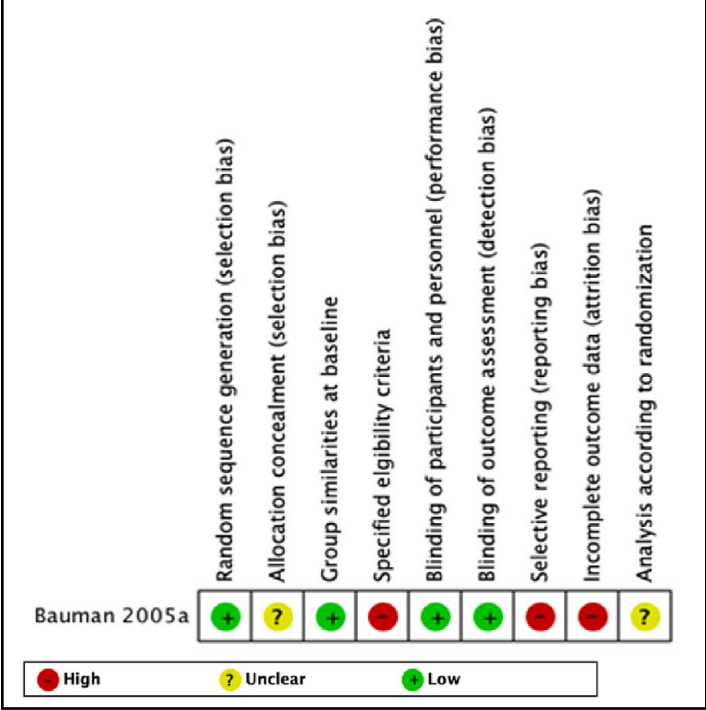


Table 7.3. Risk of bias summary for a non-randomized control trial in which alendronate was used to prevent bone loss in a cohort of individuals with acute spinal cord injury.

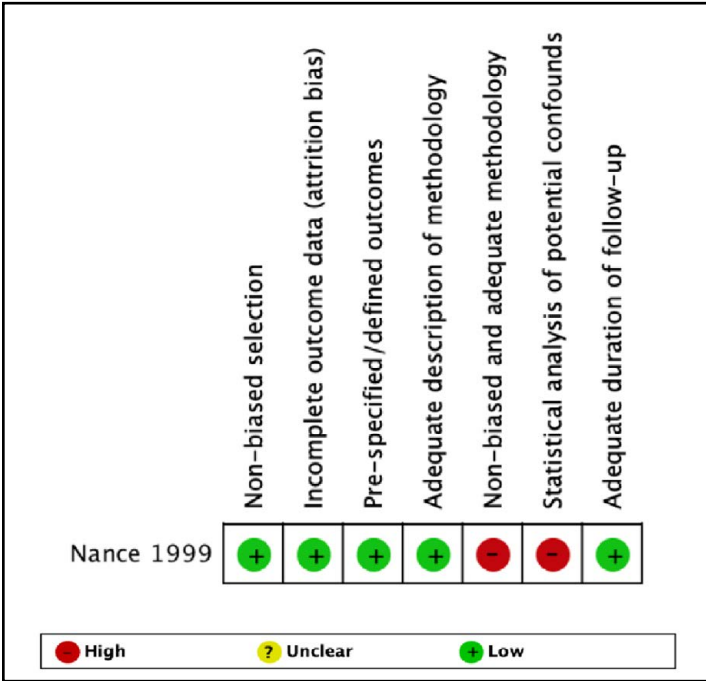


Table 7.4. Risk of bias summary for a non-randomized control trial in which zoledronic acid was used to prevent bone loss in a cohort of individuals with acute spinal cord injury.

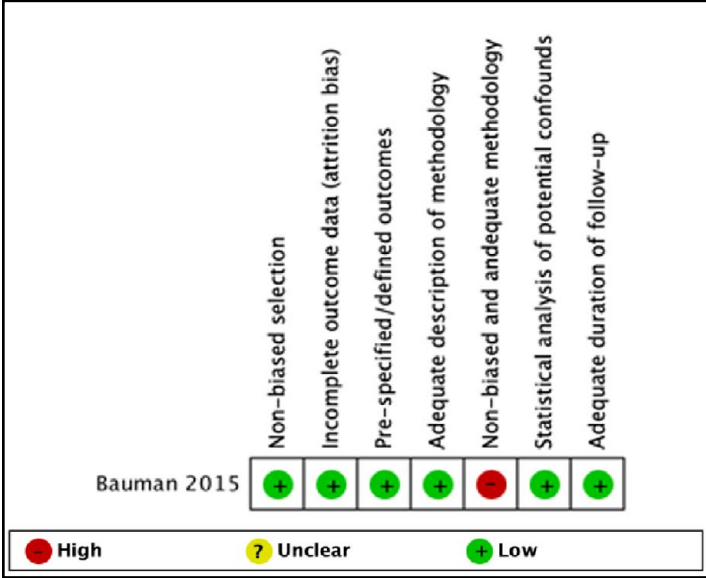


Table 7.5. Risk of bias summary for randomized controlled trials in which zoledronic acid was used to prevent bone loss in a cohort of individuals with acute spinal cord injury.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Group similarities at baseline	Specified eligibility criteria	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Selective reporting (reporting bias)	Incomplete outcome data (attrition bias)	Analysis according to randomization
Shapiro 2007	+	?	+	+	+	+	-	+	+
Bubbear 2011	+	-	+	+	-	-	-	-	?
Schnitzer 2016	+	?	-	+	+	+	+	-	?
Goenka 2018	+	+	+	+	-	+	+	+	+
Oleson 2020	+	+	+	+	+	+	-	+	+

- High
? Unclear
+ Low

Table 7.6. Risk of bias summary for a randomized controlled trial in which denosumab was used to prevent bone loss in a cohort of individuals with acute spinal cord injury.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Group similarities at baseline	Specified eligibility criteria	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Selective reporting (reporting bias)	Incomplete outcome data (attrition bias)	Analysis according to randomization
Cirnigliaro 2020	+	+	+	+	+	+	+	-	+

- High
? Unclear
+ Low

Table 7.7. Risk of bias summary for randomized controlled trials in which alendronate was used to treat bone loss in a cohort of individuals with chronic spinal cord injury.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Group similarities at baseline	Specified eligibility criteria	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Selective reporting (reporting bias)	Incomplete outcome data (attrition bias)	Analysis according to randomization
Zehnder 2004b	+	+	+	+	-	?	?	-	+
Moran de Brito 2005	?	?	+	+	?	?	?	+	?
Haider 2019	+	+	+	+	+	+	+	+	+

- High
? Unclear
+ Low

Table 7.8. Risk of bias summary for an observational study in which denosumab was used to treat bone loss among individuals with chronic spinal cord injury.

	Non-biased selection	Incomplete outcome data (attrition bias)	Pre-specified/defined outcomes	Adequate description of methodology	Non-biased and adequate methodology	Statistical analysis of potential confounds	Adequate duration of follow-up
Gifre 2016	+	+	+	+	+	-	+

- High
? Unclear
+ Low

Table 7.9. Risk of bias summary for a non-randomized control trial in which teriparatide was used to treat bone loss among individuals with chronic spinal cord injury.

	Non-biased selection	Incomplete outcome data (attrition bias)	Pre-specified/defined outcomes	Adequate description of methodology	Non-biased and adequate methodology	Statistical analysis of potential confounds	Adequate duration of follow-up
Gordon 2013	?	+	+	+	+	+	+
High Unclear Low							

Table 7.11. Risk of bias summary for randomized controlled trials in which zoledronic acid was used to treat bone loss among individuals with chronic spinal cord injury.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Group similarities at baseline	Specified eligibility criteria	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Selective reporting (reporting bias)	Incomplete outcome data (attrition bias)	Analysis according to randomization
Morse 2019	?	?	+	+	?	?			?
Varghese 2016	+	+	+	+	+	+	+	+	+
High Unclear Low									

Table 7.10. Risk of bias summary for an RCT in which teriparatide was used to treat bone loss among individuals with chronic spinal cord injury.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Group similarities at baseline	Specified eligibility criteria	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Selective reporting (reporting bias)	Incomplete outcome data (attrition bias)	Analysis according to randomization
Edwards 2018	+	+	+	+	+	+	+	+	+
High Unclear Low									

Appendix F: Putative Fracture Risk Factors

Fracture Risk Factor	HR
Anticonvulsant use ⁴³	1.16
Anticonvulsant polytherapy ⁴³	1.20
Benzodiazepine use ^{43, 45}	1.28-1.42
Heparin use ^{43, 45}	1.28-1.46
Opioid use ^{43, 44}	1.78-1.82
Tetraplegia ⁴⁵	1.27
Traumatic SCI ³⁰	1.16
Lumbar SCI	NR
Motor complete SCI ^{30, 43, 47, 48, 50}	1.34-1.70
Injury duration ^{30, 49, 52}	1.01
Charlson Comorbidity Index ³⁰	1.12
History of hip fracture 1 year prior ³⁰	4.08
History of non-hip fracture 1 year prior ³⁰	4.01
Family history of fracture ⁵¹	NR
women age $\geq$ 50 compared to older men ³⁰	1.54
CTX level ⁴⁶	NR
Factors that May Reduce Fracture Risk	HR
Thiazide diuretic use ⁴⁵	0.74
Combination therapy with thiazide diuretics and vitamin D supplementation ⁴³	0.43
Black race ^{43, 45}	0.76-0.78
Incomplete SCI ⁴³	0.57
Tetraplegia ^{30, 43}	0.79