You may also be interested in the following free CME/CE program:

www.projectsinknowledge.com/osteoPA

This year-long, continuously updated free online curriculum explores hot topics and new tools to help primary care physicians and other clinicians improve treatment of patients with or at risk for osteoporosis and fractures.

Visit www.projectsinknowledge.com for other valuable CME/CE activities.

SYLLABUS

Sunday, October 18, 2009
Philadelphia, Pennsylvania

This symposium is sponsored by Projects In Knowledge and supported by an educational donation provided by Amgen.

This is not an official program of the American College of Rheumatology.
CONTRACT FOR MUTUAL RESPONSIBILITY IN CME/CE

PROJECTS IN KNOWLEDGE WILL PROVIDE:

1. A trusting learning environment free of commercial bias.
2. An activity that has been peer-reviewed, by an expert in the field who is not a member of the faculty, to ensure that the information presented is independent, objective, scientifically rigorous, fair balanced, accurate, timely, relevant, and beneficial to patients.
3. An activity that is free of any conflicts of interest, as identified through the faculty disclosure process and resolved through our Trust In Knowledge peer review process.
4. Faculty that embrace and support our efforts.
5. Acknowledgment of off-label uses of pharmaceutical products discussed.
6. Content that will positively impact on your ability to manage your patients.
7. Ample opportunity for questions from the participants to add to the scientific rigor and real-life clinical appropriateness of information provided.
8. Access to a "Content Ombudsman" (via e-mail at ombudsmn@projectsinknowledge.com) who will handle questions on enduring materials that are not answered by this activity.
9. A dynamic learning and implementation process that meets our rigorous obligations to multiple accreditation/regulatory bodies, and that shows that Projects In Knowledge will be forever evolving and striving to do the right thing.

CLINICIANS’ RESPONSIBILITIES:

1. Be an active participant in the activity.
2. Ask questions relevant to patient care concerns.
3. Commit yourself to the entire activity time frame, because it is only then that the total learning can be experienced, utilized, and measured.
4. Allow this activity to be only a part of your total learning experience.
5. Aid in developing future activities by being a strong participant. The evaluation form assists us in this process; please give it careful professional consideration when filling it out.
6. Return to your practice and mentor the learning experience with your colleagues. Projects In Knowledge will provide extra material for this effort.

Sincerely,
Robert S. Stern
President
Projects In Knowledge, Inc.
Update on Osteoporosis for the Rheumatologist

A CME/CE Satellite Symposium

Sunday, October 18, 2009

TABLE OF CONTENTS

Program Information .................................................................................................................... 2
Faculty Biographies ....................................................................................................................... 3

AGENDA

7:00 PM – 7:15 PM  Introduction/Pathways and Targets Leading to the Prevention and Treatment of Osteoporosis and Fractures ................................................................. 7
        Jonathan D. Adachi, MD, FRCPC

7:15 PM – 7:40 PM  Who Is at Risk for Osteoporosis and Fractures? ....................... 13
        Michael J. Maricic, MD

7:40 PM – 8:05 PM  Strategies for Reducing Fracture Risk ............................................. 20
        E. Michael Lewiecki, MD, FACP, FACE

8:05 PM – 8:30 PM  Challenges and Controversies in Managing Your Osteoporosis Patients ......................................................................................................................... 27
        Nancy E. Lane, MD

8:30 PM – 8:45 PM  Q&A
        Faculty Panel
Update on Osteoporosis for the Rheumatologist

Target Audience
This CME/CE activity is designed for rheumatologists and other clinicians involved in the care of patients with or at risk of developing osteoporosis and fractures.

Activity Goal
The goals of this CME/CE activity are to address gaps in competence and practice performance by:

- Stressing the importance of early screening and diagnosis of patients with or at risk of developing osteoporosis and fractures
- Identifying the pathways involved in the pathophysiology of osteoporosis and fractures
- Providing optimal strategies for prevention and treatment of osteoporosis based on current and emerging therapies with regard to mechanism of action, efficacy, safety, and treatment regimen requirements for compliance
- Simulating case studies commonly seen in rheumatology practices

Learning Objectives
- Apply understanding of pathophysiology, risk factors, and diagnostic methodology to osteoporosis/fracture assessment to improve screening and diagnosis, and facilitate early intervention.
- Contrast mechanisms of action of current and emerging antiresorptive, anabolic, and dual-action osteoporosis/fracture prevention therapies on bone physiology/remodeling to guide treatment selection and improve patient outcomes.
- Formulate osteoporosis and fracture prevention/treatment regimens that include current antiresorptive and anabolic agents based on an analysis of the efficacy, safety, dosing, and administration of these therapies, side effect management, patient profile, and current guidelines.
- Analyze strategies that integrate emerging osteoporosis and fracture prevention/treatment regimens in patients at risk for or with osteoporosis/fractures when these agents are approved by the FDA—including antiresorptive agents, anabolic agents, and dual-action bone agents.
- Integrate monitoring techniques into practice for compliance, response to treatment, and changes in patients (eg, secondary causes of osteoporosis) to ensure interventions that improve outcomes.

CME Information: Physicians

Statement of Accreditation
Projects In Knowledge® is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Credit Designation
Projects In Knowledge designates this educational activity for a maximum of 1.75 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

CE Information: Nurses

Projects In Knowledge® (PIK) is an approved provider of continuing nursing education by the Delaware Nurses Association, an accredited approver by the American Nurses Credentialing Center’s Commission on Accreditation. PIK provider code: 080903-PROV.

Projects In Knowledge is also an approved provider by the California Board of Registered Nursing, Provider Number CEP-15227.

This activity is approved for 1.75 nursing contact hour(s).

DISCLAIMER: Accreditation refers to educational content only and does not imply ANCC, DNA, CBRN, or PIK endorsement of any commercial product or service.

CE Information: Pharmacists

Projects In Knowledge® is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education.

This program has been planned and implemented in accordance with the ACPE Criteria for Quality and Interpretive Guidelines. This satellite symposium is worth up to 1.75 contact hours (0.175 CEUs). The ACPE Universal Program Number assigned to this application-based activity is 052-000-09-064-L01-P.

Disclosure Information
The Disclosure Policy of Projects In Knowledge requires that presenters comply with the Standards for Commercial Support. All faculty are required to disclose any personal interest or relationship they or their spouse/partner have with the supporters of this activity or any commercial interest that is discussed in their presentation. Any discussions of unlabeled/unapproved uses of drugs or devices will also be disclosed in the course materials.

For complete prescribing information on the products discussed during this CME/CE activity, please see your current Physicians’ Desk Reference (PDR).

Jonathan D. Adachi, MD, FRCPC, has received honoraria and has received consulting fees and/or is on the advisory board of Amgen Inc, Bristol-Myers Squibb, Eli Lilly and Company, GlaxoSmithKline, Hoffmann-La Roche Inc., Merck, Novartis Pharmaceuticals Corporation, Nycomed, Pfizer Inc, Procter & Gamble, Sanofi-Aventis, Servier, and Wyeth.

Nancy E. Lane, MD, has received grant/research support from Nordic Bioscience, Pfizer Inc, and Procter & Gamble; has received honoraria from Amgen Inc and Eli Lilly and Company; and has received consulting fees and/or is on the advisory board of Merck and Zosano Pharma® Inc.

E. Michael Lewiecki, MD, FACE, FACE, has received grant/research support from Amgen Inc, Eli Lilly and Company, GlaxoSmithKline, Novartis Pharmaceuticals Corporation, Pfizer Inc, Procter & Gamble, Hoffmann-La Roche Inc, Merck, Novartis Pharmaceuticals Corporation; on the advisory board of Amgen Inc, Eli Lilly and Company, GlaxoSmithKline, Hoffmann-La Roche Inc, and Novartis Pharmaceuticals Corporation; on the speakers bureau of Eli Lilly and Company, GlaxoSmithKline, Hoffmann-La Roche Inc, and Novartis Pharmaceuticals Corporation, Amgen Inc, Eli Lilly and Company, Hoffmann-La Roche Inc, Novartis Pharmaceuticals Corporation, Upsher-Smith Laboratories Inc, and Wyeth; is a direct stock shareholder with General Electric, Procter & Gamble, and Teva Pharmaceuticals; and is on the board of directors of International Society for Clinical Densitometry.

Michael J. Marici, MD, has received grant/research support from Amgen Inc, Eli Lilly and Company, Hoffmann-La Roche Inc, and Novartis Pharmaceuticals Corporation; and has received honoraria and consulting fees from Amgen Inc, Eli Lilly and Company, Hoffmann-La Roche Inc, Novartis Pharmaceuticals Corporation, and Procter & Gamble.

Karen Gravelle, PhD, Content Editor, has no significant relationships to disclose.

Peer Reviewer has no significant relationships to disclose.

Projects In Knowledge's staff members have no significant relationships to disclose.

Conflicts of interest are thoroughly vetted by the Executive Committee of Projects In Knowledge. All conflicts are resolved prior to the beginning of the activity by the Trust In Knowledge peer review process.

The opinions expressed in this activity are those of the faculty and do not necessarily reflect those of Projects In Knowledge.

This CME/CE activity is provided by Projects In Knowledge solely as an educational service. Specific patient care decisions are the responsibility of the clinician caring for the patient.

There is no fee for this activity.

This independent CME/CE activity is supported by an educational donation provided by Amgen.

Projects In Knowledge is a registered trademark of Projects In Knowledge, Inc.
Biographies

Chair

Jonathan D. Adachi, MD, FRCPC
Professor, Department of Medicine
St. Joseph’s Healthcare
McMaster University
Hamilton, Ontario
Canada

Jonathan D. Adachi, MD, FRCPC, is a professor of medicine at McMaster University and the Director of the Hamilton Arthritis Centre at St. Joseph’s Healthcare in Hamilton, Ontario, Canada. He is a graduate of McMaster University and received his fellowship in internal medicine and in rheumatology. Dr. Adachi has conducted many clinical trials and has published extensively on a wide variety of therapies for the prevention and treatment of corticosteroid-induced and postmenopausal osteoporosis. As a result of his expertise he has participated in the development of guidelines for the treatment of postmenopausal and corticosteroid-induced osteoporosis.

In addition to his clinical studies, Dr. Adachi has been interested in noninvasive imaging of bone and cartilage. As a result of this interest he has participated in studies of bone densitometry, peripheral CT, and peripheral MRI as modalities for investigating bone and joint diseases. Studies of bone microarchitecture using pQCT and 1T pMRI by Dr. Adachi and his co-investigators have highlighted its ability to predict failure load and fracture risk in both cadaveric studies and in clinical samples. Their bone geometry studies were later used to demonstrate gender differences in trabecular bone geometry with aging as well as differences in bone geometry in the dominant and nondominant wrists. In a study of isolated radii that investigated the same parameters using both pQCT and high-resolution MRI, trabecular porosity explained 25% to 30% of the variance in mechanical failure load in addition to bone mineral density. The use of pMRI for assessing trabecular bone structure in vivo was further demonstrated in a group of volunteers where age-related changes were shown for both connectivity index and mean hole area. From these works, they have demonstrated feasibility of bone structure quantification from pQCT and pMRI. More studies are planned to learn about patterns of bone loss with aging in women, and how they relate to fractures.

As a result of his interests, Dr. Adachi has published more than 244 peer-reviewed journal articles, 453 peer-reviewed abstracts, 19 book chapters, and has had 519 peer-reviewed presentations. He is a well-recognized national and international speaker.

Dr. Adachi started his career with the first annual Phillip Rosen Award in Rheumatology when he completed his training in rheumatology. More recently Dr. Adachi was awarded the Lindy Fraser Award by Osteoporosis Canada. In 2006, he was awarded the Alliance for Better Bone Health Chair in Rheumatology at McMaster University and received the North American Menopause Society Award for Innovations in Osteoporosis Research. He has recently been elected to the Board of Directors of the International Osteoporosis Foundation.
Update on Osteoporosis for the Rheumatologist

Faculty

Nancy E. Lane, MD
Director and Endowed Professor
Aging Center, Medicine and Rheumatology
University of California at Davis Medical Center
Sacramento, California

Nancy E. Lane, MD, is Endowed Professor of Medicine and Director of the Center for Healthy Aging at the University of California, Davis (UCD) Medical Center. She received her undergraduate degree from UCD, where she graduated with highest honors and was awarded the Department of Biochemistry Citation. After earning her medical degree from the University of California, San Francisco, she completed her residency in medicine at Mount Zion Hospital and Medical Center and a clinical fellowship in rheumatology at the Palo Alto Veterans Administration Hospital and Stanford University Medical Center. She is board certified in internal medicine and rheumatology.

A nationally recognized expert in the medical management of osteoporosis, Dr. Lane participated in groundbreaking studies with parathyroid hormone (PTH) and the pathobiology of bone fragility. She is a fully funded NIH researcher on osteoporosis and bone health. Her special areas of expertise include the use of PTH for the treatment of glucocorticoid-induced osteoporosis and the genetics epidemiology of hip osteoarthritis in elderly women and men.

Dr. Lane is the president of the US Bone and Joint Decade Board and a member of numerous professional organizations, including the American College of Rheumatology, the American Society of Bone and Mineral Research, the Orthopedic Research Society, the Association of Osteobiology, and the Society of Clinical Immunology. She is a consultant reviewer for numerous peer-reviewed journals, among them JAMA, Journal of Bone and Mineral Research, Annals of Internal Medicine, and Journal of Bone and Joint Surgery. Dr. Lane also serves on the editorial boards of Osteoporosis International, Arthritis Research, Journal of Bone and Mineral Research, Nature Clinical Practice Rheumatology, and Journal of Musculoskeletal Medicine. In addition, Dr. Lane is co-editor of Arthritis and Rheumatism, and associate editor of Primer of Metabolic Bone Diseases.

A frequent lecturer and presenter on osteoporosis and the author of hundreds of journal articles, book chapters, and abstracts, Dr. Lane has written The Osteoporosis Book: A Guide for Patients and Their Families and co-authored All About Osteoarthritis: The Definitive Resource for Arthritis Patients and Their Families.
Biographies

Faculty

E. Michael Lewiecki, MD, FACP, FACE
Osteoporosis Director
New Mexico Clinical Research & Osteoporosis Center
Clinical Assistant Professor of Medicine
University of New Mexico School of Medicine
Albuquerque, New Mexico

E. Michael Lewiecki, MD, FACP, FACE, is clinical assistant professor of medicine at the University of New Mexico School of Medicine and Director of the New Mexico Clinical Research & Osteoporosis Center. He is a consultant in osteoporosis and metabolic bone disease, supervisor and interpreter of bone density studies at his center, and an educator with a special interest in the management of osteoporosis and metabolic bone disease. He is principal investigator for the center’s osteoporosis clinical trials and author of many peer-reviewed scientific publications on osteoporosis and bone densitometry.

Dr. Lewiecki is past-president of the International Society for Clinical Densitometry (ISCD). He is a faculty member for the ISCD educational programs in bone densitometry, vertebral fracture assessment, and management of osteoporosis, and is on the Editorial Board of the Journal of Clinical Densitometry. He has received national and international awards, including “Young Internist of the Year” by the American Society of Internal Medicine in 1986, “Physician of the Year” by the ISCD in 2002, the ISCD “Paul D. Miller Service Award” in 2006, and the “Laureate Award” of the New Mexico Chapter of the American College of Physicians in 2006.

He is a fellow of the American College of Physicians and the American College of Endocrinology. Dr. Lewiecki is president and founder of the Osteoporosis Foundation of New Mexico and director of its educational activities. He is past-president of the New Mexico Society of Internal Medicine and past-president of New Mexico Medical Group. He established and is program director of the annual Santa Fe Bone Symposium.

Dr. Lewiecki, who was raised in the Boston area, is a graduate of Amherst College and Northwestern University Medical School. He completed postgraduate training in internal medicine at the University of New Mexico Health Sciences Center and is board-certified in internal medicine. After serving 2 years as a medical officer in the United States Air Force, he settled in Albuquerque, where he has remained ever since.
Update on Osteoporosis for the Rheumatologist

Faculty

Michael J. Maricic, MD  
Clinical Associate Professor of Medicine  
University of Arizona School of Medicine  
Co-director of Catalina Pointe Clinical Research  
Tucson, Arizona

Michael J. Maricic, MD, is co-director of Catalina Pointe Clinical Research in Tucson, Arizona. He is a clinical associate professor of medicine at the University of Arizona School of Medicine.

While at the University of Arizona, Dr. Maricic served as Head of the Section of Rheumatology and as Program Director for both the Internal Medicine Residency and the Rheumatology Fellowship Programs. He has chaired both the Curriculum Committee and the Graduate Medical Education Advisory Committee. Dr. Maricic has received the Dean’s Teaching Award for Excellence, the Virginia Furrow Award for Excellence in Graduate Medical Education, and was elected AOA by the Medical Student Class. The Internal Medicine Housestaff named him the Outstanding Attending in both 2003 and 2004.

Dr. Maricic is a fellow of the American College of Rheumatology and a past Chairman of its Educational Materials and Audiovisual Aids Committees. He is a member of the American Society for Bone and Mineral Research, a past member of the National Osteoporosis Foundation Newsletter Editorial Board, and past Associate Editor of the *Journal of Clinical Densitometry* and currently serves on its Editorial Board.

He has authored 38 peer-reviewed articles on osteoporosis and rheumatology, numerous chapters, and has co-edited the textbook, *Decision Making in Internal Medicine*, and the book, *Bone Disease in Rheumatology*. 
Vertebral fractures are common in men and women. Significant morbidity and mortality is associated with both hip and spine fractures. Despite this knowledge, there is a significant treatment care gap associated with both types of fractures. For the rheumatologist and for their patients, a major concern is corticosteroid-induced osteoporosis.

Anticatabolic agents, in particular bisphosphonates, have been the treatments of choice. Newer therapies looking at different targets have been investigated. Recent studies have focused on the relationship between the RANK/RANK ligand/OPG pathway and its regulation of bone remodeling. Treatment based on our understanding of this pathway has been developed with the advent of a new treatment option, denosumab. Another target is cathepsin K inhibition. Studies investigating the use of cathepsin K inhibition are ongoing.

Studies to date have focused on anticatabolic agents. PTH is the only anabolic therapy currently available. Bone morphogenic protein is another anabolic agent that is being studied. New targets are currently being investigated based on our understanding of signals that stimulate bone formation. In particular, Wnt, sclerostin, and DKK-1 are potential targets for treatment.

As our understanding of bone biology expands further, targets for therapeutic intervention may be identified.

Suggested Readings

Update on Osteoporosis for the Rheumatologist

Slides produced as of October 8, 2009 (may not reflect final presentation)

Introduction: Pathways and Targets Leading to the Prevention and Treatment of Osteoporosis and Fractures
Jonathan D. Adachi, MD, FRCPC
Professor, Department of Medicine
St. Joseph’s Healthcare
McMaster University
Hamilton, Ontario
Canada

Program
- Introduction/Pathways and Targets Leading to the Prevention and Treatment of Osteoporosis and Fractures
  – J.D. Adachi, MD
- Who Is At Risk for Osteoporosis and Fractures?
  – Michael Maricic, MD
- Strategies for Reducing Fracture Risk
  – E. Michael Lewiecki, MD
- Challenges and Controversies in Managing Your Osteoporosis Patients
  – Nancy E. Lane, MD

Prevalence of Vertebral Deformity
The Canadian Multicentre Osteoporosis Study

Mortality from The Canadian Multicentre Osteoporosis Study
- Hip fracture: 1 in 4 die within 5 years of fracture
- Vertebral fracture: 1 in 6 die within 5 years of fracture
- No fracture: 1 in 12 die within 5 years of follow-up

CaMos HUI3 Scores—Baseline Differences Between Diseases

Percentage of Participants on Therapy
Clinical Vertebral Fracture

Abbreviations: CaMos, Canadian Multicentre Osteoporosis Study; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus.
Introduction/Pathways and Targets Leading to the Prevention and Treatment of Osteoporosis and Fractures

Jonathan D. Adachi, MD, FRCPC

Slides produced as of October 8, 2009 (may not reflect final presentation)

Corticosteroid-Induced Osteoporosis

Relative Risk for Fracture by Steroid Dose


Corticosteroid-Associated Adverse Events—What Are Patients Concerned About?

Adverse Event | Preference Value (0–1)
--- | ---
Hip fracture requiring nursing home stay | 0.55
Vertebral fracture – chronic pain | 0.58
Hip fracture – uncomplicated | 0.61
Septic arthritis | 0.63
Vertebral fracture – acute | 0.65
Ulcuer requiring hospitalization | 0.68
New onset diabetes | 0.69
Rib fracture | 0.77

Preference value anchors are 1 = “current health”; 0 = “death”.

Graphic courtesy of Dr. J. D. Adachi.

Corticosteroid-Induced Osteoporosis

Relative Risk for Fracture by Time on Steroids

Corticosteroid-Associated Adverse Events and Matched Historical Cohort

| Adverse Event          | User (112) | Nonuser (112) |
--- | --- | ---
Fracture | 21 | 8
Cataract | 17 | 5
Serious infection | 14 | 4
GI bleed or ulcer | 11 | 4
Diabetic complication | 8 | 3
Herpes zoster | 8 | 1
Myocardial infarction | 4 | 4
Stroke | 6 | 1
Glaucoma | 1 | 1
Death | 2 | 0


Pathways and Targets Leading to the Prevention and Treatment of Osteoporosis and Fractures
Bisphosphonates Localize to the Bone Surface and Inhibit Bone Resorption

Osteoblasts

OPG

Activated Osteoclast

BP-coated bone surface

Bone Resorption

Bisphosphonates Bind With High Affinity to Hydroxyapatite in Bone

Sites of Action for Currently Available Pharmacologic Agents

Precursors

Prefusion Osteoclast

Multinucleated Osteoclast

RANK ligand

RANK

Hormones

Cytokines

Growth Factors

Bisphosphonate Uptake Into Osteoclast During Resorption

Activated Osteoclast

Bone Resorption

RANK

OPG

Bisphosphonates Lead to Dysfunctional Osteoclasts

The RANK/RANKL/OPG Concept

RANK

• Expressed by osteoclasts and their precursors
• Activated by RANKL binding

RANKL

• Signaling protein expressed by osteoblasts/bone lining cells
• Binds to RANK and promotes osteoclast formation, function, and survival

OPG

• Protein secreted by osteoblasts/bone lining cells
• Natural inhibitor of RANKL
• Blocks RANKL signaling to balance bone remodeling

The RANKL/RANK/OPG Pathway Regulates Bone Remodeling

Estrogen Limits the Release of RANK ligand

Hormones

Growth factors

Cytokines

OPG Binds to Excess RANK ligand

OPG

Many Factors Stimulate Osteoblast Expression of RANKL

Glucocorticoids

Vitamin D

IL-11

IL-6

PTH

IL-1

PGE2

Estrogen

OPG Decoy Receptor Prevents RANKL Binding to RANK: Inhibits Osteoclast Formation, Function, and Survival

Decay Receptor and Formation Are Balanced

OPG Binds to Excess RANK ligand

Bone Formation

Bone Resorption Inhibited

Osteoclast Formation, Function, and Survival Inhibited

Osteoblasts

Mature Osteoclast

OPG

Bone Resorption

Prefusion Osteoclast

OPG

RANK

OPG

CFU-M

RANK

OPG

Bone Resorption and Formation Are Balanced

OPG

RANK

OPG

RANK ligand

OPG

Bone Formation

Activates Osteoclast

M-CSF, macrophage colony-stimulating factor; PTH, parathyroid hormone; PTHrP, parathyroid-related hormone; TNF, tumor necrosis factor.


Abbreviations: OPG, osteoprotegerin; RANKL, RANK ligand.
Introduction/Pathways and Targets Leading to the Prevention and Treatment of Osteoporosis and Fractures
Jonathan D. Adachi, MD, FRCPC

Slides produced as of October 8, 2009 (may not reflect final presentation)

Resorbing Osteoclast

Signals Determining Differentiation Toward Osteoblasts and Acting on Mature Osteoblasts to Enhance Bone Formation

After Wnt binding to its receptor (frizzled) and coreceptors (low density lipoprotein-related proteins 5 and 6 [LRP5 and LRP6]), disheveled, an intracellular protein is induced to degrade GSK-3β. In addition, the cytoplasmic tails of LRP5 and LRP6 bind and anchor axin. These 2 events lead to the stabilization of β-catenin and its translocation to the nucleus, where it binds to T-cell factor 4 (TCF-4) or lymphoid enhancer binding factor1 (LEF-1) to regulate transcription.

Under the influence of Wnt and BMP, undifferentiated mesenchymal cells differentiate toward cells of the osteoblast lineage. PTH enhances cell replication, and PTH and growth hormone induce the synthesis of insulin-like growth factor I, which enhances osteoblastic bone formation.

Signals Pathways Used by BMPs in Osteoblasts

Basal Conditions

Under basal conditions β-catenin is phosphorylated by glycogen synthase kinase 3β (GSK-3β), axin, and adenomatous polyposis coli (APC) tumor suppressor protein and degraded in the proteasome.

Wnt Antagonists

The extracellular Wnt antagonists prevent Wnt signaling. Dikkopf-1 (Dkk-1) in association with Kremen and sclerostin bind LRPS and LRPS. Soluble frizzled-related protein (sFRP-1) binds Wnt and prevents its interaction with frizzled.

Abbreviation: BMP, bone morphogenic protein; PTH, parathyroid hormone.
## Summary

- Osteoporosis is common and is relevant to the rheumatologist
- It results in significant morbidity and mortality
- It is a major concern to our patients

## Summary

- Advances in our understanding of bone biology have led to the discovery and use of a wide variety of therapies
- Recent discovery of the RANK/RANKL/OPG pathway has resulted in a new therapy
- Future therapies may arise from our understanding of signaling pathways that inhibit the osteoclast and stimulate the osteoblast
Who Is at Risk for Osteoporosis and Fractures?

Michael J. Maricic, MD

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that affects more than 2 million people in the United States. Consequences to the patient include pain, reduced quality of life, increased work disability, and increased mortality. Osteoporosis and fractures are more common in patients with RA and significantly increase morbidity.

Bone loss occurs early in RA, even in patients not on glucocorticoids (GC). Gough et al measured bone density in RA patients not on GC and found significantly different bone loss at the hip and spine after only 12 months.

Factors associated with systemic bone loss in RA include systemic and local inflammation due to inflammatory cytokines, glucocorticoids and other immunosuppressive medications, age, gonadal deficiency, and immobility (functional status).

A number of cytokines regulate osteoclastic bone loss in RA. Those that stimulate osteoclastic resorption include RANKL (receptor activator nuclear factor-κB ligand), M-CSF (macrophage-colony stimulating factor), PGE2 (prostaglandin E2), TNF-α (tumor necrosis factor-α), interleukins 1, 6, 7, 15, and 17, PTH (parathyroid hormone), PTHrP (PTH-related protein), and vitamin D. Those that inhibit bone resorption include OPG (osteoprotegerin), GM-CSF (granulocyte monocyte-colony stimulating factor), interferon γ, and interleukins 4, 12, and 18.

RANKL appears to play an essential role in the link between chronic inflammation and bone loss, both systemically and in the joint. T-cells and fibroblast-like synoviocytes (FLS) are major cell types expressing RANKL in RA synovial tissue. Through RANKL, T-cells and FLS drive osteoclast differentiation and bone erosions. High systemic levels of RANKL in RA patients also play an important role in the link between inflammation and systemic bone loss.

Glucocorticoid-induced osteoporosis (GIOP) is the second most common form of osteoporosis in the world, and the most common iatrogenic form. GC initially induce increased osteoclastic bone resorption by increasing RANKL and decreasing OPG production. Subsequently, the major effects of GC on bone are inhibition of bone formation and increased apoptosis of both osteoblast and osteocytes.

Bone loss is rapid following initiation of GC, and fracture risk is increased even at doses <2.5 mg of prednisolone. Fracture risk increases within 3 months of starting GC, then falls following discontinuation of GC, but not back to baseline. Thus, ever use of systemic glucocorticoids independently increases the risk of fracture, even if the patient is no longer on glucocorticoids.

Suggested Readings

Slide 1

Who Is At Risk for Osteoporosis and Fractures?

Michael J. Maricic, MD
Clinical Associate Professor of Medicine
University of Arizona School of Medicine
Co-director of Catalina Pointe Clinical Research
Tucson, Arizona

Slide 2

Osteoporosis and Fractures in Rheumatoid Arthritis

Osteoporosis and fractures significantly increase the morbidity of patients with rheumatoid arthritis


Slide 3

Types of Bone Loss in Rheumatoid Arthritis
- Erosions—at joint margins in areas of direct pannus invasion
- Periarticular osteopenia—adjacent to inflamed joints
- Generalized osteoporosis—of the axial and appendicular skeleton

Goldring SR, Crotti TN. In: Bone Disease in Rheumatology. Lippincott Williams & Wilkins;2005:8-14.

Slide 4

Most Rheumatoid Arthritis Patients Develop Bone Erosions During First 2 Years of Disease

Patients with rheumatoid arthritis <1 year underwent annual radiologic assessment of hands and feet.
Graphics courtesy of Dr. Michael Maricic.

Slide 5

Early Bone Loss In Rheumatoid Arthritis
- Bone mineral density (BMD) measured over first 2 years, before glucocorticoids or disease-modifying anti-rheumatic drug therapy
- No difference in BMD at baseline between patients and controls
- Difference in BMD at 12 months
  - Spine -2.4 vs -0.6%
  - Trochanter -4.3 vs -0.4%


Slide 6

Factors Associated with Systemic Bone Loss in Rheumatoid Arthritis
- Systemic and local inflammation due to inflammatory cytokines
- Glucocorticoids and other medications
- Age
- Gonadal deficiency
- Immobility (functional status)
Who Is At Risk for Osteoporosis and Fractures?

Michael J. Maricic, MD

Slides produced as of October 8, 2009 (may not reflect final presentation)

Slide 7

### Increased Frequency of Reduced BMD in Males with RA

<table>
<thead>
<tr>
<th>Age Group (Years)</th>
<th>BMD (g/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29</td>
<td>0.97</td>
</tr>
<tr>
<td>30-39</td>
<td>0.93</td>
</tr>
<tr>
<td>40-49</td>
<td>0.89</td>
</tr>
<tr>
<td>50-59</td>
<td>0.89</td>
</tr>
<tr>
<td>60-70</td>
<td>0.85</td>
</tr>
</tbody>
</table>

Abbreviations: BMD, bone mineral density; RA, rheumatoid arthritis; SD, standard deviation.


### Increased Frequency of Spine and Hip Osteoporosis in Females with Rheumatoid Arthritis

<table>
<thead>
<tr>
<th>Age Group (Years)</th>
<th>BMD (g/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29</td>
<td>0.92</td>
</tr>
<tr>
<td>30-39</td>
<td>0.87</td>
</tr>
<tr>
<td>40-49</td>
<td>0.84</td>
</tr>
<tr>
<td>50-59</td>
<td>0.82</td>
</tr>
<tr>
<td>60-70</td>
<td>0.79</td>
</tr>
</tbody>
</table>

Abbreviations: BMD, bone mineral density; RA, rheumatoid arthritis; SD, standard deviation.


Slide 8

### Fractures in RA Patients

**ARAMIS Study**

- **Males with Prednisone >5 mg/d (n = 25)**
- **Females with Prednisone >5 mg/d (n = 46)**

**Years from Study Entry**

- **Presence of Osteoporosis (n = 20)**
- **Probability of Remaining Fracture Free**

- **0.8**
- **0.6**
- **0.4**
- **0.2**
- **0.0**


Slide 9

### Cytokine Regulation of Bone Resorption in RA

**Stimulatory**

- RANKL
- M-CSF
- TNFα
- IL-1q and -p
- IL-6, -7, -15, and -17
- PGE₂
- PTH
- PTHrP
- Vitamin D

**Inhibitory**

- OPG
- IL-4
- IL-12
- IL-18
- GM-CSF
- IFN


Slide 10

### Osteoclasts Are Present at Sites of Bone Cartilage Interface in RA

- Unmineralized cartilage
- Mineralized cartilage
- Cortical bone-cartilage interface
- Osteoclast


Slide 11

### Essential Role of RANKL in RA—Link Between Chronic Inflammation and Bone Loss

- Through RANKL, T-cells and FLS drive osteoclast differentiation and bone erosion in the joint
- T-cells and FLS are major cell types expressing RANKL in RA synovial tissue
- RANKL expression supported by other proinflammatory cytokines
  - Including TNF, IL-1, IL-6, IL-17, PGE₂

Abbreviations: FLS, fibroblast-like synoviocytes; IL, interleukin; PGE₂, prostaglandin E₂; RA, rheumatoid arthritis; RANK, receptor activator of nuclear factor (κB) ligand; TNF, tumor necrosis factor.


Slide 12
Osteoarthritis and Fractures

Patients with radiographic hip and/or knee osteoarthritis have higher adjusted levels of bone mineral density, but have no difference in the rate of fractures. Among older women in the Study of Osteoporotic Fractures with radiographic hip osteoarthritis, there was no difference in the risk of both hip and vertebral fractures, over a mean follow-up of 7.4 years.


Fractures in Ankylosing Spondylitis

- Cumulative prevalence 10%–20% in ankylosing spondylitis
- Mainly thoracic spine involved
- Peripheral bony fractures not increased
- Reported fracture prevalence in AS patients

<table>
<thead>
<tr>
<th>Mean Age</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>34 y</td>
<td>9.5% vs 3.4% (Cooper 1994)</td>
</tr>
<tr>
<td>38 y</td>
<td>16.7% vs 2.6% (Mitra 2000)</td>
</tr>
<tr>
<td>41 y</td>
<td>18% (Ralston 1990)</td>
</tr>
</tbody>
</table>

- Relative risk for vertebral fractures increased 6- to 8-fold


Osteoarthritis and Fractures

- Patients with radiographic hip and/or knee osteoarthritis have higher adjusted levels of bone mineral density, but have no difference in the rate of fractures
- Among older women in the Study of Osteoporotic Fractures with radiographic hip osteoarthritis, there was no difference in the risk of both hip and vertebral fractures, over a mean follow-up of 7.4 years.


Fractures in Systemic Lupus

- In a retrospective study of 702 women with lupus with a total of 5951 person-years, the risk of fracture was noted to be increased (OR = 4.7) in the lupus cohort compared with controls of similar age
  - Older age at lupus diagnosis and longer duration of glucocorticoid use seemed to be independent determinates of fractures
- In another study of 242 patients with systemic lupus erythematosus, age and reduced bone mineral density, but not glucocorticoid use, predicted fracture risk


Bone Loss in Systemic Lupus

- The prevalence of low bone mass in systemic lupus erythematosus varies from 15%–46% (osteopenia) to 6%–15% (osteoporosis) in different studies
- This prevalence varies according to the site of measurement (lumbosacral spine, total hip, femoral neck), gender, and age of the patient studied
- Decreases in both cortical and trabecular bone have been reported
- Low bone mineral density is evidenced in both early and late disease


Osteoporosis in Ankylosing Spondylitis

- Technically challenging to detect
- Predominantly confined to the axial skeleton
- Vertebral osteoporosis is a common complication of ankylosing spondylitis, with a prevalence between 18.7% and 62% in various series

Who Is At Risk for Osteoporosis and Fractures?

Michael J. Maricic, MD

**Glucocorticoid-Induced Osteoporosis (GIOP)**
- GIOP is the second most common form of osteoporosis in the world, and the most common iatrogenic form
- 0.2% of adults receive prednisone on a long-term basis (>500,000 adults in United States)
- Most common reasons are rheumatoid arthritis and chronic obstructive pulmonary disease

**Fractures Are the Most Common Serious Adverse Event of Glucocorticoids**

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>User (n = 112)</th>
<th>Nonuser (n = 112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fracture</td>
<td>21 (19%)</td>
<td>8 (7%)</td>
</tr>
<tr>
<td>Cataract</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>Serious infection</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>GI bleed or ulcer</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Diabetic complication</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Stroke</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Death</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>


**Dose Relationship of Fracture Risk with Glucocorticoids**
- Chart review from General Practice Database in United Kingdom
- Steroid users matched by age, gender, and clinical practice
- ~60% female, mean age 57 years

**Pathophysiology of GIOP—Bone Formation and Resorption**

**Rapid BMD Decline Due to Glucocorticoids in Rheumatoid Arthritis**


**Fracture Risk Is Increased Even at Doses <2.5 mg Prednisolone**

Effect of Daily Glucocorticoid Dose on Nonvertebral Fractures

Fracture Risk in GIOP Increases on Treatment, Then Quickly Reverts When GCs Are Discontinued

Incidence of Vertebral Fracture in Postmenopausal Patients Receiving GCs Compared with Nonusers of GCs

Predictors of Vertebral Fracture in Postmenopausal Patients Receiving Oral Glucocorticoid Therapy—Results

Risk Factors for Hip Fracture in Men and Women

- Compared with nonusers of GCs, patients receiving GCs were younger, had a higher BMD at baseline, and had fewer prevalent fractures
- Nevertheless, the risk of fracture was higher in the GC users compared with nonusers (adjusted RR 5.67, 95% CI 2.57–12.54)

Abbreviations: GCs, glucocorticoids; GIOP, glucocorticoid-induced osteoporosis.
Who Is At Risk for Osteoporosis and Fractures?

Michael J. Maricic, MD

Slides produced as of October 8, 2009 (may not reflect final presentation)

FRAX—Factors That Independently Increase the Risk of Hip Fractures in Addition to Age and Femoral Neck T-Score

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>RR</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior fracture after 50 years</td>
<td>1.62</td>
<td>(1.30–2.01)</td>
</tr>
<tr>
<td>Parental history of hip fracture</td>
<td>2.28</td>
<td>(1.48–3.51)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>1.60</td>
<td>(1.27–2.02)</td>
</tr>
<tr>
<td>Ever systemic corticosteroids</td>
<td>2.25</td>
<td>(1.60–3.15)</td>
</tr>
<tr>
<td>Alcohol intake &gt;2 drinks daily</td>
<td>1.70</td>
<td>(1.20–2.42)</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>1.73</td>
<td>(0.94–3.20)</td>
</tr>
</tbody>
</table>

Conclusions

- Patients with inflammatory arthritis, especially rheumatoid arthritis, are at increased risk for osteoporosis and fractures
- These risks are significantly increased in those patients taking glucocorticoids

The management of osteoporosis begins with assessment of fracture risk by bone density testing in appropriately selected patients and consideration of clinical risk factors for fracture. Patients with low bone density should be evaluated for contributing factors (e.g., vitamin D deficiency, hypogonadism, glucocorticoid use, malabsorption), and treated to correct these, when possible. All patients, regardless of fracture risk, may benefit from discussion of the importance of healthy lifestyle and good nutrition for skeletal health: regular physical activity, adequate intake of calcium and vitamin D, and avoidance of tobacco smoking, excess alcohol, and medications known to have adverse skeletal effects. The National Osteoporosis Foundation (NOF) recommends a daily intake of at least 1200 mg elemental calcium with diet plus supplements, if needed, and vitamin D3 800 to 1000 IU/day. Many elderly patients may require a higher dose of vitamin D3 to achieve a desirable serum 25-hydroxyvitamin D level of at least 30 ng/mL. Patients at high fracture risk should be considered for pharmacologic therapy to reduce fracture risk. The NOF guidelines recommend consideration of pharmacologic therapy to reduce fracture risk for postmenopausal women or men age 50 years and older in any of the following circumstances: (a) T-score is -2.5 or below at the lumbar spine or femoral neck, or (b) personal history of vertebral (clinical or morphometric) or hip fracture, or (c) low bone mass (osteopenia, T-score between -1.0 and -2.5 at the femoral neck or lumbar spine) with 10-year probability of hip fracture ≥3% or 10-year probability of major osteoporotic fracture (hip, spine, proximal humerus, distal forearm) ≥20% using the US adaptation of the World Health Organization fracture risk algorithm, FRAX.

Approved drugs may be classified according to their effect on bone turnover. Those that act primarily by reducing bone turnover (antiresorptive or anticatabolic agents) include oral bisphosphonates (alendronate, risedronate, ibandronate), injectable bisphosphonates (ibandronate, zoledronate), an oral estrogen agonist/antagonist (raloxifene), and an intranasal biologic agent (salmon calcitonin). A single drug that increases bone turnover (a bone anabolic agent), recombinant human parathyroid hormone (1-34) (teriparatide), is approved for the treatment of osteoporosis in the United States. It is not known with certainty whether any of these drugs is more effective at reducing fracture risk or is safer than any other for the treatment of postmenopausal osteoporosis, since no head-to-head clinical trials with fractures as the primary endpoint have been completed. Factors to consider in the decision to use a specific drug include a patient’s comorbidities, preferences, previous drug experiences, availability, and cost. The potential benefits and risks must be discussed with the patient before starting therapy, with regular follow-up contact to assure tolerance, compliance, persistence, and response to therapy.

Emerging drugs for the treatment of osteoporosis include agents with novel mechanisms of action (denosumab, odanacatib, antibody to sclerostin), new estrogen agonist/antagonists (lasofoxifene, bazedoxifene), new delivery systems for existing drugs (salmon calcitonin, teriparatide), and drug combinations given concurrently, sequentially, or cyclically.

Suggested Readings
Strategies for Reducing Fracture Risk

E. Michael Lewiecki, MD, FACP, FACE
Osteoporosis Director
New Mexico Clinical Research & Osteoporosis Center
Clinical Assistant Professor of Medicine
University of New Mexico School of Medicine
Albuquerque, New Mexico

Universal Recommendations

- Regular weight-bearing exercise
- Fall prevention
- Avoid tobacco use and excess alcohol
- Identification and treatment of risk factors for fracture
- Elemental calcium at least 1200 mg/day
- Vitamin D3 800–1000 IU/day

National Osteoporosis Foundation
Treatment Guidelines

Fracture Risk Assessment

Intervention Threshold

Treatment Decisions

Follow-Up
Vitamin D

- Serum 25-OH-D levels should be measured in patients at risk for vitamin D deficiency
- Serum 25-OH-D level should be at least 30 ng/mL
- Many patients need more than 800–1000 IU per day to achieve a desirable level
- Many elderly patients are at high risk for vitamin D deficiency
- Intake >2000 IU per day is safe and necessary for some patients

Abbreviations: FRAX, Fracture Risk Assessment; NOF, National Osteoporosis Foundation.

NOF Treatment Guidelines

Postmenopausal women and men age 50 and older with the following should be considered for treatment:

**Osteoporosis**
- T-score ≤-2.5 at femoral neck (FN) or lumbar spine (LS) after evaluation for secondary causes, or
- Hip or vertebral (clinical or morphometric) fracture

**Osteopenia**
- T-score between -1.0 and -2.5 at FN or LS, and
- Fracture Risk Assessment (FRAX)

10-year probability of hip fracture ≥3% or major osteoporotic fracture ≥20%

ACR Guidelines for GIO

**Beginning treatment with prednisone ≥5 mg/day for ≥3 months.**
- Baseline bone mineral density and repeat every 6–12 months
- Modify risk factors (smoking, alcohol)
- Weight-bearing exercise
- Calcium & vitamin D
- Bisphosphonate
  - Use with caution in premenopausal women


**Established treatment with prednisone ≥5 mg/day for ≥3 months.**
- Modify risk factors (smoking, alcohol)
- Weight-bearing exercise
- Calcium & vitamin D
- Hormone replacement therapy, if deficient
- If T-score <1.0, start bisphosphonate (use calcitonin as second-line agent)
- If T-score normal, repeat bone mineral density every 1–2 years.


Using FRAX and NOF Guide

- FRAX is validated in
  - Untreated women and men between the age of 40 and 90 years
  - White, black, Hispanic, Asian in United States
- NOF guide uses FRAX for treatment decisions in
  - Untreated postmenopausal women and men age 50 and older with osteopenia who do not qualify for treatment based on other treatment indications
- Do NOT use FRAX with the NOF guide in
  - Patients who meet other treatment indications
  - T-score normal or osteoporosis
  - Premenopausal women, men younger than age 50, children

Old Guide vs New Guide

<table>
<thead>
<tr>
<th>Case</th>
<th>Old Guide</th>
<th>New Guide</th>
</tr>
</thead>
</table>
| 55-year-old White woman (120 lbs, 5'2") with T-score = -2.1 | Treat (T-score <2.0) | Don't treat (10-year risk of major fracture 10%, hip 1.5%)
| 80-year-old White woman (120 lbs, 5'2") with T-score = -1.1 | Treat (T-score ≥1.5) | Treat (10-year risk of major fracture 24%, hip 2.4%)

Abbreviations: FRAX, Fracture Risk Assessment; NOF, National Osteoporosis Foundation.

Graph courtesy of Dr. E. M. Lewiecki.
Strategies for Reducing Fracture Risk

E. Michael Lewiecki, MD, FACP, FACE

Slide 13

Benefits of NOF Guide

- Improved selection of patients most likely to benefit from therapy
  - Fewer “young” patients with slightly low BMD and low risk treated
  - More “old” patients with slightly low BMD and high risk treated
- Better use of limited healthcare resources
- Application beyond postmenopausal White women

Slide 14

Limitations of NOF Guide

- Cost-effectiveness modeling may be irrelevant if drug cost is extremely low
- May be used inappropriately to restrict pharmacy benefits
- Conflicting recommendations for treatment if FRAX is used when BMD is normal or osteoporosis
- May identify patients for treatment with little or no evidence of benefit (T-score >-1.5)

Slide 15

Fracture Risk Assessment

Intervention Threshold

Treatment Decisions (whom to treat and how to treat)

Follow-Up

Slide 16

Decision to Treat

- Public health factors
  - Fracture probability (FRAX)
  - Cost-effectiveness (NOF Guide)
- Patient factors
  - Efficacy and safety for individual patient
  - Nonskeletal risks and benefits
  - Comorbidities
  - Expected adherence to therapy
  - Patient beliefs and preferences
  - Insurance coverage/affordability

Slide 17

Laboratory Evaluation

- Complete blood count
- Blood chemistries
  - Creatinine
  - Calcium
  - Phosphorus
  - Albumin
  - Alkaline phosphatase
  - Liver enzymes
- 24-hour urine for calcium, sodium, and creatinine
- Thyroid-stimulating hormone
- Celiac antibodies
- Testosterone
- Follicle-stimulating hormone
- Urinalysis
- Serum protein electrophoresis, immunofixation, light chains
- Parathyroid hormone
- 25-OH-vitamin D
- Urinary free cortisol
- Dexamethasone suppression

Slide 18

FDA Indications for Osteoporosis

<table>
<thead>
<tr>
<th>Drug</th>
<th>PMO Prevention</th>
<th>PMO Treatment</th>
<th>GIO (Women, Men) Prevention</th>
<th>GIO (Women, Men) Treatment</th>
<th>Men Prevention</th>
<th>Men Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alendronate PO</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risedronate PO</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibandronate PO</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bazedronate IV</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zoledronate IV</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcitonin N</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raloxifene PO</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teriparatide SC</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Graphic courtesy of Dr. E. M. Lewiecki.
Clinical Challenges After Starting Treatment

- Motivating the patient to fill the prescription, take medication correctly, regularly, and for a sufficient amount of time to benefit
- Determining how (or if) to follow and monitor the patient to assure that benefit is achieved
- Deciding when (if ever) to stop or change therapy
- Knowing when (if ever) to restart, if treatment is stopped
- Managing side effects, perceived side effects, and fear of side effects

Improving Adherence to Therapy

- Longer dosing intervals
- Less complex administration
- Injectable therapy?
- Patient education
- Ongoing communication
- Nurse monitoring

Fracture Risk Reduction in Randomized Controlled Trials

<table>
<thead>
<tr>
<th>Medication</th>
<th>Spine</th>
<th>Nonvertebral</th>
<th>Hip</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alendronate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risedronate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibandronate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zoledrionate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salmon Calcitonin</td>
<td>~</td>
<td>~</td>
<td></td>
</tr>
<tr>
<td>Raloxifene</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teriparadite</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Monitor with Biomarkers

<table>
<thead>
<tr>
<th>LSC * with 95% CI</th>
<th>DXA Bone Mineral Density</th>
<th>Bone Turnover Marker</th>
</tr>
</thead>
<tbody>
<tr>
<td>~3% (Must be measured for each facility)</td>
<td>~20%–40% (biologic and analytic variability)</td>
<td></td>
</tr>
</tbody>
</table>

| Signal-noise ratio (biologic change/LSC) | ~1 | ~1 |

<table>
<thead>
<tr>
<th>Time to reach LSC</th>
<th>1–2 years (varies by skeletal site and drug)</th>
<th>3 months (within several days for some drugs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicare coverage</td>
<td>1–2 years (varies by Medicare carrier)</td>
<td>2 baseline, 1 follow-up per year</td>
</tr>
</tbody>
</table>

Guidelines for clinical use

- Yes
- No

FLEX—Incidence of Fractures

- ALN/PLB (n = 437)
- ALN/ALN (n = 442)

<table>
<thead>
<tr>
<th>Fracture Incidence</th>
<th>% Fracture Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>11%</td>
<td>10%</td>
</tr>
<tr>
<td>19%</td>
<td>19%</td>
</tr>
<tr>
<td>3%</td>
<td>3%</td>
</tr>
</tbody>
</table>

Abbreviations: ALN, alendronate; PLB, placebo.

*Least Significant Change = smallest change in a measurement that is likely to represent a genuine change and not a measurement error or biologic variation.

Graphic courtesy of Dr. E. M. Lewiecki.
Strategies for Reducing Fracture Risk
E. Michael Lewiecki, MD, FACP, FACE

When to Consider an Alendronate Holiday

- When patient never needed treatment in the first place
  - Retrospective application of NOF guide
- After good response (bone mineral density/bone turnover marker) to at least 5 years treatment and fracture risk no longer high
  - No fracture, T-score >-2.5, “young”
- Continue treatment in high-risk patients
  - Previous fractures, T-score -2.5 and below

Emerging Therapy

- Antiresorptive (anti-catabolic)
  - Denosumab
  - Lasofoxifene
  - Bazedoxifene
  - CE/bazedoxifene
  - Odanacatib
  - New delivery systems

- Osteo-anabolic (bone-forming)
  - Sclerostin inhibitor
  - Variations of parathyroid hormone
  - Calcium-sensing receptor antagonist (calcilytic)
  - New delivery systems
  - Combinations of antiresorptive and anabolic

When to End a Bisphosphonate Holiday

- Not clear
- Possible approaches
  - Arbitrarily restart treatment after 1–2 years
  - Monitor BMD/BTM every 6–12 months and restart treatment when significant decrease in BMD or increase in BTM
- Reconsider treatment plan if fracture or change in clinical status

Denosumab for Postmenopausal Osteoporosis

- BMD
  - Lumbar spine † 9.2% (P < .0001)
  - Total hip † 6.0% (P < .0001)
- BTMs
  - CTX † 72% (P < .001)
- Fracture risk
  - Verterbral † 68% (7.2% placebo vs 2.3% denosumab, P < .0001)
  - Hip † 40% (1.2% placebo vs 0.7% denosumab, P = .036)
  - Nonvertebral † 20% (8.0% placebo vs 6.5% denosumab, P = .011)

FREEDOM Safety—Adverse Events

Update on Osteoporosis for the Rheumatologist

**FREEDOM Safety—Serious Adverse Events**

<table>
<thead>
<tr>
<th>SAEs</th>
<th>Denosumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>25.8%</td>
<td>25.1%</td>
</tr>
<tr>
<td>Infections</td>
<td>4.1%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Cancer</td>
<td>3.7%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.7%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Deaths</td>
<td>1.8%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Cardiovascular events</td>
<td>4.8%</td>
<td>4.6%</td>
</tr>
</tbody>
</table>

SAEs in at least 0.1% of subjects with \( P < 0.01 \)

<table>
<thead>
<tr>
<th>SAEs</th>
<th>Denosumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concussion</td>
<td>&lt;0.1%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>0.3%</td>
<td>&lt;0.1%</td>
</tr>
</tbody>
</table>

Abbreviation: SAEs, serious adverse events.

**Other Denosumab Studies**

- Phase 2 trial: Effects on bone mineral density (BMD) and bone turnover markers (BTMs) are reversible with discontinuation, with a robust response to retreatment\(^1\)
- DEFEND: Increases BMD and reduces BTMs in postmenopausal women with osteopenia\(^2\)
- DECIDE: In patients initiating treatment, those taking denosumab increase BMD and decrease BTMs more than those taking alendronate\(^3\)
- STAND: In patients previously treated with alendronate, those switching to denosumab increase BMD more than those continuing alendronate\(^4\)


**Denosumab for Rheumatoid Arthritis**

- 12-month randomized controlled trial of denosumab 60 or 180 mg q6mo vs placebo in rheumatoid arthritis patients on methotrexate
- Primary endpoint: MRI erosion score at 6 months
- Secondary endpoint: modified Sharp erosion score at 12 months
- Results: decreased erosion scores with denosumab; no effect on joint space narrowing; comparable adverse events


**Lasofoxifene for Postmenopausal Osteoporosis**

- **Efficacy**
  - Increases BMD, reduces BTMs, decreases risk of vertebral and nonvertebral fractures
  - Decreases risk of ER+ breast cancer
  - Improves signs and symptoms of vulvovaginal atrophy
- **Safety**
  - Increases risk of VTEs, hot flushes, muscle spasm, and vaginal bleeding


**Bazedoxifene for Postmenopausal Osteoporosis**

- **Efficacy**
  - Increases BMD, reduces BTMs, and decreases risk of vertebral fractures
- **Safety**
  - Increases risk of VTEs, hot flushes, muscle cramps


**Summary**

- BMD + clinical risk factors (CRFs) predict fracture risk better than BMD or CRFs alone
- NOF guide better identifies patients for cost-effective intervention to reduce fracture risk
- Optimal use of these tools requires full understanding of their benefits and limitations
- Treatment decisions must consider all known clinical factors using good judgment
Challenges and Controversies in Managing Your Osteoporosis Patients

Nancy E. Lane, MD

The evaluation of patients for osteoporosis and the continued follow-up of treatment efficacy can be very challenging. In this short talk, we will review four clinical cases that emphasize the importance of careful evaluation and follow-up in optimizing patients’ bone health. The cases include an 80-year-old woman on long-term antiresorptive therapy who has experienced significant bone loss over the past few years, a 69-year-old man with prostate cancer who is being treated with androgen deprivation therapy, a 72-year-old woman with osteoporosis who is initiating teriparatide therapy, and a 28-year-old woman with rheumatoid arthritis who is receiving glucocorticosteroids. These case discussions provide examples of the issues encountered in determining osteoporosis treatment and offer some thoughtful guidance.

Suggested Readings

Case 1
Bone Loss in 80-Year-Old Female on Chronic Alendronate Treatment

Mrs. W

- 80-year-old woman was diagnosed with postmenopausal osteoporosis on 6/2/98 with L1-L4 T-score = -2.5 at age 72
- Baseline evaluation showed normal reactive oxygen species, normal physical examination, and normal complete blood count, comprehensive metabolic panel, C-reactive protein, urinalysis
- Started on alendronate 6/98 and continued ever since
- Patient says she is taking alendronate regularly and correctly, with daily calcium and multivitamin

BMD Response to Therapy

- Lumbar spine bone mineral density (BMD) increase of 6.8% after 4 years of therapy
- 2 years later (6 years after beginning alendronate) BMD decreased by 4.8% (>least significant concentration): evaluation showed normal CBC, and low serum 25-OH-D (25 ng/mL) – treated and corrected
- BMD continued to decline at annual rate of 2%–3%

Evaluation for Secondary Osteoporosis After 11 Years of Bisphosphonate Treatment

- No cardiac, pulmonary, GI, or renal symptoms
- Normal physical examination
- Normal CMP, CRP, P, urinalysis
- CBC normal except high mean corpuscular volume of 105 (normal folate and B12 level)
- 25-OH-D 25 ng/mL, despite adequate vitamin D3 supplementation
- Fasting serum NTX 15.0 nM BCE
- Serum protein electrophoresis–polyclonal increase in gamma fraction
- Endomysial Ab IgA high at 1:1280 (normal <1:10)
- A procedure was performed

Endoscopy with Small Bowel Biopsy 5/21/09

- “Duodenal mucosa with moderate to severe villous atrophy and marked intraepithelial lymphocytosis consistent with gluten-induced enteropathy”
- Started on gluten-free diet
- Additional vitamin D3 1000 IU/day
- Alendronate continued
Challenges and Controversies in Managing Your Osteoporosis Patients

Nancy E. Lane, MD

Slides produced as of October 8, 2009 (may not reflect final presentation)

Slide 7

Biopsy of Celiac Disease

Slide 8

Case 2

Patient with Prostate Cancer Receiving Androgen Deprivation Therapy

Slide 9

Mr. H

- A 69-year-old white male is discovered to have metastatic (stage IV) prostate cancer and chooses to undergo androgen deprivation therapy (ADT) rather than orchiectomy
- Does ADT have an impact on his bone health?

Slide 10

Bone Loss During Initial Therapy for Prostate Cancer

Slide 11

Fracture-Free Survival Diminishes with Time and Cumulative Use of GnRH

Slide 12

2008 NOF Synopsis of Major Recommendations

When to Perform BMD Testing

A. In women age 65 years and older, and men age 70 years and older, recommend BMD testing

B. In postmenopausal women and men age 50–70 years, recommend BMD testing when you have concern based on their risk factor profile

Fracture-Free Survival Diminishes with

Time and Cumulative Use of GnRH

2008 NOF Synopsis of Major Recommendations

When to Perform BMD Testing

A. In women age 65 years and older, and men age 70 years and older, recommend BMD testing

B. In postmenopausal women and men age 50–70 years, recommend BMD testing when you have concern based on their risk factor profile

Fracture-Free Survival Diminishes with

Time and Cumulative Use of GnRH

2008 NOF Synopsis of Major Recommendations

When to Perform BMD Testing

A. In women age 65 years and older, and men age 70 years and older, recommend BMD testing

B. In postmenopausal women and men age 50–70 years, recommend BMD testing when you have concern based on their risk factor profile

Fracture-Free Survival Diminishes with

Time and Cumulative Use of GnRH

2008 NOF Synopsis of Major Recommendations

When to Perform BMD Testing

A. In women age 65 years and older, and men age 70 years and older, recommend BMD testing

B. In postmenopausal women and men age 50–70 years, recommend BMD testing when you have concern based on their risk factor profile

Fracture-Free Survival Diminishes with

Time and Cumulative Use of GnRH

2008 NOF Synopsis of Major Recommendations

When to Perform BMD Testing

A. In women age 65 years and older, and men age 70 years and older, recommend BMD testing

B. In postmenopausal women and men age 50–70 years, recommend BMD testing when you have concern based on their risk factor profile

Fracture-Free Survival Diminishes with

Time and Cumulative Use of GnRH

2008 NOF Synopsis of Major Recommendations

When to Perform BMD Testing

A. In women age 65 years and older, and men age 70 years and older, recommend BMD testing

B. In postmenopausal women and men age 50–70 years, recommend BMD testing when you have concern based on their risk factor profile
2008 ISCD Indications for BMD Testing

- Adults with a disease or condition associated with low bone mass or bone loss
- Adults taking medications associated with low bone mass or bone loss
- Anyone being considered for pharmacologic therapy
- Anyone being treated, to monitor treatment effect
- Anyone not receiving therapy in whom evidence of bone loss would lead to treatment

Treatment of Low Bone Density in Men with Prostate Cancer About to Undergo Androgen Deprivation Therapy

- At what bone density should treatment with a bone active agent begin?
- What should he be treated with?

Treatment of Bone Loss in Men Treated with Androgen Deprivation Therapy

- Oral bisphosphonates
  - Alendronate 70 mg weekly
  - Risedronate 35 mg weekly or 150 mg monthly
- Teriparatide contraindicated?
- Zoledronate 4 mg IV q3mo
- Denosumab 60 mg SQ q6mo (In the future?)

Mean Percentage Change in BMD from Baseline to 6 and 12 Months


Mean Percentage Change in BMD from Baseline over 24 Months

Challenges and Controversies in Managing Your Osteoporosis Patients

Nancy E. Lane, MD

Slides produced as of October 8, 2009 (may not reflect final presentation)

Current Osteoporosis Medications

- Calcium carbonate 1000 mg/day
- Vitamin D 800 IU/day
- Nasal calcitonin 3 x per week

Mrs. F

72-year-old postmenopausal woman with a fragility fracture of her right wrist and lumbar spine T-score of -3.0

Work-up for secondary causes of osteoporosis was negative

What Are the Key Clinical Pearls/Take-Aways from this Case?

- Low bone density and osteoporosis are common in men undergoing androgen deprivation therapy (ADT) for prostate cancer, even before ADT
- ADT accelerates bone loss and increases fracture risk
- The bisphosphonates are effective treatments for preventing bone loss in men treated with ADT, and may reduce the heightened risk of fractures

**Phase III Trial—Denosumab in the Treatment of Bone Loss in Patients Undergoing ADT for Nonmetastatic Prostate Cancer**

- Primary endpoint
  - Change in BMD at 24 months
- Secondary endpoint
  - Fractures (both vertebral and nonvertebral)

*Current or prior IV bisphosphonates administration was not allowed.


**Denosumab in Patients Undergoing Androgen Deprivation Therapy**

<table>
<thead>
<tr>
<th></th>
<th>Denosumab (n = 734)</th>
<th>Placebo (n = 734)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine BMD at 24 mo</td>
<td>+5.6%</td>
<td>-1.0%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>New vertebral fractures at 36 mo</td>
<td>1.5%</td>
<td>3.9%</td>
<td>.006</td>
</tr>
</tbody>
</table>


**Case 3**

Postmenopausal Woman with Fragility Fracture

Slide 19

Slide 20

Slide 21

Slide 22
Treatment Recommendations

- Discontinue calcitonin
- Start teriparatide 20 μg/day SC (a bisphosphonate would be inappropriate as she has already had a fracture, despite having been on an antiresorptive agent)
- Patient attended teriparatide education program to learn how to give injections and information about therapy
- Baseline laboratory tests ordered
- Serum calcium, second morning urine for calcium/creatinine ratio, P1NP, CTX-1

Laboratory Test Results

- P1NP – 48 mg/mL
- Serum calcium – 7.0
- Urine calcium/creatinine – 0.1 mg/mg

Follow-Up Visit—3 Months Later

- Patient became nauseated after the PTH injections, so they were switched to evening injections, every other day and over 4 weeks, after which she was able to tolerate daily injections
- Vital signs were normal and she had evidence of mild erythema around the injection sites on her thighs

Laboratory Data After 3 Months of rhPTH (1-34)

- Serum calcium – 8.0 mg/dL
- Urine calcium/Cr – 0.1 mg/mg
- P1NP – 50 ng/mL

No Change in P1NP After 3 Months of Treatment

- Ask about injections
  - Patient gave herself injections every day in her thigh

Modification of Treatment

- Instruct patient to give herself the injections into the abdomen and to move the injection site around to different areas of the abdomen
- ABSORPTION OF SUBCUTANEOUS INJECTIONS MAY BE MORE EFFECTIVE AT ABDOMEN COMPARED WITH THE EXTREMITIES FOR PTH
- You ask the patient to return to the clinic in one month for another P1NP laboratory test
**Month 4 of rhPTH (1-34)**

One month after switching the injection site from the thighs to the abdomen
- P1NP: 100 ng/mL
- Serum calcium: 8.1 mg/dL
- Urine calcium/cr: 0.13 mg/mg

**Case 3—Summary**

- Absorption of rhPTH (1-34) is greater at the abdomen than the upper arm or thigh
- By changing the injection site and rechecking the P1NP, we improved this patient’s chances of having a positive response to PTH treatment
- If we had waited until a bone mineral density test was done, possibly at 1 year but probably at after 2 years of treatment, she may have add a less optimal response to the treatment
- Examination of the P1NP after 1–3 months provided useful information to the clinician that resulted in modification of how the patient administered the therapy

**Case 4**

**Rheumatoid Arthritis Patient Receiving Glucocorticosteroids**

**Mrs. L**

- 28-year-old premenopausal woman
- Rheumatoid arthritis, age of onset, 21 years
- Complications of her RA include
  - Osteonecrosis of hip from prednisone
  - Pulmonary involvement
  - Vasculitis

**Investigations**

- Positive rheumatoid arthritis factor >1:640
- Antinuclear antibody test + 1:160 speckled pattern, low C3 and C4
- Positive anti-DNA, anti-Sm, anti-SSA, anti-SSB
- CRP 7
- Anti-cyclic citrullinated peptide antibody -50
- X-ray of hands and feet show erosion, osteopenia, and deformities
Further History of Bone Health

- No family history of osteoporosis
- ≤1 serving of dairy products per day
- Adequate outdoor sun exposure
- Menarche age 12/regular cycles prior to prednisone dose >30 mg/day
- Appetite and weight stable

Current Treatment

- Prednisone 10–30 mg daily (x 6 months)
  - Currently 15 mg daily
- Hydroxychloroquine 400 mg daily
- Methotrexate 20 mg/wk
- Folic acid 1 mg/daily
- Etanercept

Laboratory Data

- Vitamin D: 20 ng/mL
- Calcium normal
- PTH normal
- TFTs normal
- Estradiol <40 pmol/L
- Progesterone <1 nmol/L
- Follicle-stimulating hormone 3U/L
- Luteinizing hormone <1 U/L
- Creatinine and blood urea nitrogen normal
- Bone mineral density
  - Spine -2.0 T-score
  - Hip -2.5 T-score

Osteoporotic Therapies in Women of Childbearing Age

- Are there any issues with osteoporotic therapies in women of childbearing age?

Bisphosphonates in Premenopausal Females—Issues

- Animal studies have identified skeletal changes
- FDA Category C pregnancy risk – contraindicated during pregnancy
- Preconception exposure bisphosphonate case reports have not identified any developmental or bone density abnormalities
- Lower birth weight, lower gestational age at birth, and higher rates of spontaneous abortion have been reported (but confounding factors affect interpretation)


Osteoporosis Management in Mrs. L

- Combination of calcium carbonate and vitamin D
- Risedronate 35 mg weekly
- Consider denosumab when it is approved, since it is given every 6 months and does not accumulate in the bone
Challenges and Controversies in Managing Your Osteoporosis Patients

Nancy E. Lane, MD

Slides produced as of October 8, 2009 (may not reflect final presentation)

Conclusions/Summary

- Secondary causes of osteoporosis is a rapidly growing entity
- Bone loss in individuals undergoing hormone ablation therapy for cancer, on glucocorticoids, and with celiac disease can be identified and prevented
Update on Osteoporosis for the Rheumatologist

Notes:

__________________________________________________________________________________________
__________________________________________________________________________________________
__________________________________________________________________________________________
__________________________________________________________________________________________
__________________________________________________________________________________________
__________________________________________________________________________________________
__________________________________________________________________________________________
__________________________________________________________________________________________
__________________________________________________________________________________________
__________________________________________________________________________________________
__________________________________________________________________________________________
__________________________________________________________________________________________
__________________________________________________________________________________________
__________________________________________________________________________________________
You may also be interested in the following free CME/CE program:

This year-long, continuously updated free online curriculum explores hot topics and new tools to help primary care physicians and other clinicians improve treatment of patients with or at risk for osteoporosis and fractures.

[Link to program]

Visit [Link to site] for other valuable CME/CE activities.