Novel Approaches to Managing Osteoporosis

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Potential Conflicts of Interest

- **Rich Marasco, in the past two years, has served/serves as a consultant to:**
  - Abbott, Amgen, BI
- **Rich Marasco serves/has served on the speakers bureau of, or has received money speaking at programs or working on projects sponsored by:**
  - Abbott, Amgen, Jansen, J&J Long Term Care Group, Novartis, Pfizer, Merck, Astellas
- **Rich's company, Seniorpharm.com, LLC has received educational grants from:**
  - Allergan, Astellas, Eisai, Forest, Lilly, Novo Nordisk, Ortho Biotech, sanofi-aventis, Watson

Learning Objectives

- ***At the conclusion of this knowledge-based activity, each participant will be able to:***
- Review the medical impact and pathophysiology of osteoporosis
- Identify risk factors for developing osteoporosis
- Identify risk factors for osteoporotic fracture
- Review the pathophysiology of osteoporosis and it's impact on physical and psychosocial functioning and life expectancy
- Evaluate the efficacy, safety and tolerability of the most frequently prescribed therapies
- Evaluate lifestyle modification that can potentially reduce the risk of fracture

Learning Objectives (shared)

- ***At the conclusion of this knowledge-based activity, each participant will be able to:***
- Contrast the pathophysiology of fractures in patients with CKD to those with age-related or postmenopausal osteoporosis
- Discuss appropriate diagnosis of bone disease in patients with CKD
- Describe the current management of bone fractures in CKD
- Analyze the fracture risk post kidney transplantation and discuss appropriate treatment intervention

Biochemical Markers of Bone Metabolism

- In Chronic Kidney Disease
  - Phosphorus
  - Parathyroid Hormone
  - Calcium
  - Other Electrolytes
  - Total Alkaline Phosphatase or bone specifc alkaline phosphatase (an osteoblast activity marker)
  - 1,25 dihydroxyvitamin D
- In Postmenopausal Osteoporosis
  - Serum or urine collagen cross-links N-telopeptide (NTx) and C-telopeptide (CTx), markers of bone resorption
  - Bone specifc alkaline phosphatase (an osteoblast activity marker)
  - Serum osteocalcin, a bone formation marker
  - Propeptide type 1 collagen (P1NP) a marker of osteoblast activity
  - 25-hydroxyvitamin D levels

How is Osteoporosis Diagnosed

- Stage 1-3 of CKD
  - T score ≤ -2.5
  - Fragility fractures
- Stage 4-5 of CKD
  - Diagnosis is not straightforward or defined
  - In Stage 5 (and especially for those in dialysis) hip fracture risk may be 4 times higher then in aged-matched controls

Ball AM, Gillen DL, Sherrard D, et al. Risk of hip fracture among dialysis and renal transplant recipients. JAMA 2002; 288:3014-3018

Treating Osteoporosis in CKD

- Stage 1-2 CKD
- Bisphosphonate or Teriparatide are currently the first line considerations
- Caution is needed and closer monitoring for adverse events should be performed
- Cautious dosing is "required"

- Stage 4-5 CKD
- Treatment decisions are more difficult
- No prospective data is available showing any approved/available medications effective if ClCr is <30 ml/min
- Evaluate the risks and benefits of treating "off label"

Osteoporosis

- Definition: porous bone
  - Most common bone disease among adults in the United States
  - Bone tissue mass and architecture deteriorate, leading to bone fragility and an increased risk for fracture
  - Osteoporosis fractures occur most frequently in the hip, spine or wrist, but can affect any bone
- In the United States 44 million people have osteoporosis
  - This is half of all adults aged 50 and older
- Another 34 million have osteopenia (where bones are weakened)
- Osteoporosis risk is higher in women than in men; and in Asians or Caucasians than in Hispanics or Blacks
- > 2 million fractures occurring annually in the United States are related to osteoporosis

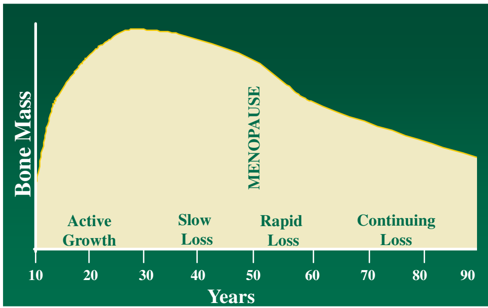
National Osteoporosis Foundation, Clinicians Guide to Prevention and Treatment of Osteoporosis. 2008 www.nof.org/professionals/NOF_Clinicians_Guide.pdf

Pathophysiology

- Throughout life bones go thru two processes:
  - Formation (Formation of new bone: done by Osteoblasts
  - Resorption (Breaking down of old bone) done by Osteoclasts
- During youth and adolescence the rate of bone formation exceeds resorption, so bones grow and increase in density
- In our 20's bones usually reach their peak mass and new bone formation begins to slow
- About midlife (30's-40's) resorption begins to overtake formation and net bone loss occurs

US Department of Health and Human Services Office of the Surgeon General. Bone Health and Osteoporosis: A Report of the Surgeon General. www.surgeongeneral.gov/library/bonehealth/content.html

Bone Mass in Women



Adapted from Wasnich, R.D. et al.: *Osteoporosis: Critique and Practicum*, Honolulu, Banyan Press, 1989, pp. 179-213.

Primary VS Secondary Osteoporosis

- **Primary**
  - Occurs later in life
  - Characterized as:
- Type 1
  - (Postmenopausal Osteoporosis)
- Type 2
  - (Senile Osteoporosis)

- **Secondary**
  - Caused by other conditions or exposures
  - Occurs at any age

Primary Osteoporosis

- Type 1
  - AKA: Postmenopausal Osteoporosis
  - Occurs when estrogen levels decline
  - Occurs in 5-20% of women
  - Usually occurs a few years after the onset of menopause
  - Significantly greater risk for women than men
- Type 2
  - AKA: Senile Osteoporosis
  - Occurs in very old (≥70)
  - Twice as likely in women as men
  - Exacerbated by age-related Vitamin D synthesis reduction or reduced Vitamin D activity
  - In older women both Type 1 & 2 frequently occur together

Secondary Osteoporosis

- Caused by many conditions and exposures
- Many medications lead to bone loss
  - Glucocorticoids (most predominant)
  - Ankylating chemotherapeutic agents (Cisplatin)
  - Antiepileptics
  - Cyclosporin A
  - Diuretics
  - Excess thyroid hormone replacement
  - Gonadotropin-releasing hormone agonist (leuprolide/Lupron™)

National Osteoporosis Foundation, Clinicians Guide to Prevention and Treatment of Osteoporosis. 2008 www.nof.org/professionals/NOF_Clinicians_Guide.pdf

Glucocorticoid Risk Exposure

- Exposure of at least 5 mg Prednisolone Daily for at least 3 months is a risk factor
- Glucocorticoid Equivalents:
  - Betamethasone 0.6 mg
  - Cortisone 25 mg
  - Dexamethasone 0.75 mg
  - Fludracortisone 1.3 mg
  - Hydrocortisone 20 mg
  - Methylprednisolone 4 mg
  - Prednisone 5 mg
  - Triamconolone 4 mg

National Osteoporosis Foundation, Clinicians Guide to Prevention and Treatment of Osteoporosis. 2008 www.nof.org/professionals/NOF_Clinicians_Guide.pdf

Other Causes of Secondary Osteoporosis

- **Lifestyle Factors**
  - Anorexia Nervosa
  - Excessive Alcohol Intake
  - Excessive Protein Intake
  - Smoking
- **Endocrine Disorders**
  - Cushing's Syndrome
  - Hyperparathyroidism
  - Hyperthyroidism
  - Hypergonadism
  - Type 1 Diabetes Mellitus
- **Neoplastic Condition**
  - Multiple Myeloma
- **Systemic Diseases**
  - Ankylosing Spondylitis
  - Gaucher's Disease
  - Mastocytosis
  - Psoriasis
  - Rheumatoid Arthritis
- **Organ Dysfunction**
  - Asthma
  - Celiac Sprue
  - COPD
  - Cystic Fibrosis
  - Inflammatory Bowel Disease
  - Organ Transplantation
  - Primary Biliary Cirrhosis
  - Renal Failure

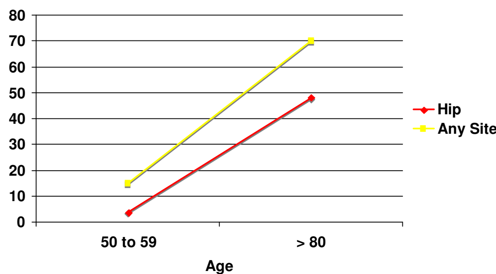
Templeton K, Secondary Osteoporosis. J Am Acad Orthop Surg. 2005;13(7):475-486

Epidemiology of Osteoporosis

- Technical definition of Osteoporosis is a bone mineral density (BMD) level >2.5 standard deviations below the youth adult mean
- Meet this definition **and** have had a fracture = ***established*** or ***severe osteoporosis***
- Prevalence of osteoporosis depends on the site of BMD measurement:
  - 17% postmenopausal, caucasian women have osteoporosis of the hip (12% hispanics, 8% blacks)
  - 33% when other sites (including the spine or forearm) are used for BMD measurement

Looker AC, et al; Prevalence of low femoral bone density in older US adults from NHANES III. J Bone Miner Res, 1997;12(11):1761-1768

Osteoporosis Prevalence Increases with Age



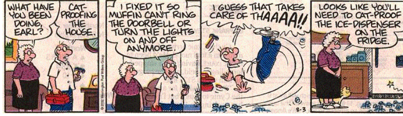
Looker AC, et al; Prevalence of low femoral bone density in older US adults from NHANES III. J Bone Miner Res, 1997;12(11):1761-1768

Osteoporosis Risk Factors

- Decreased Bone Mineral Density (BMD) is the primary clinical measure for Osteoporosis
- BMD is expressed as a "T-score" which is defined as the number of standard deviations from the mean BMD for young adults
  - T-score: -1 thru -2.5 = osteopenia
  - T-score: ≤2.5 = osteoporosis
- Sometimes a Z-score is used which is age and sex matched
  - Z-score: <-1.5 indicates factors other than aging are contributing to bone loss

BMD & T-scores & Z-scores

- Until recently BMD was the main risk factor for fractures considered in risk assessment for women (men were generally excluded)
- Researchers noticed that more than half of fragility fractures occurred on patients whose T-score was above the diagnostic threshold for osteoporosis
- Because of this additional fracture risk factors needed to be considered….



Siris ES, Chen YT, Abbott TA, et al; Bone mineral density thresholds for pharmacological intervention to prevent fractures. Arch Intern Med. 2004; 164(10):1108-1112

Additional Important Risk Factors for Osteoporosis Fractures

- Alcohol Use
- Body Mass Index
- Bone Density
- Cigarette Smoking
- Falls
- Genetics
- Hypogonadism
- Nutrition
- Physical Inactivity

World Health Organization. Prevention and Management of Osteoporosis: Report of a WHO Scientific Group. Geneva Switzerland: The World Health Organization 2003

Osteoporosis Screening & Guidelines

- In the past, BMD was the principal method for identifying patients with osteoporosis who would benefit from treatment
- 2008 National Osteoporosis Foundation (NOF) published a new guideline for identification and treatment of osteoporosis and osteoporosis fractures
  - Uses an online tool called the FRAX which estimates patients' absolute risks for hip fracture or any major osteoporotic fracture
- A recent study (Hamdy, et, al, J Clin Densitom 2009) reported that FRAX scores calculated with and without BMD would result in the same treatment decision 90% of the time in postmenopausal women

Kanis JA, Johnell O, et al; FRAX and the assessment of fracture probability in men and women from the UK. Osteoporos Int. 2008;19(4):385-397.

FRAX: Fracture Risk Assessment Tool (Determines 10 Year Fracture Risk)

http://www.sheffield.ac.uk/FRAX/tool.jsp?locationValue=9

Pharmacologic & Non-Pharmacologic Therapy

- **Pharmacologic**
- Bisphosonates
- Raloxifene
- Teriparatide
- Estrogen
- Calcitonin
- RANK Ligand

- **Non-Pharmacologic**
- Calcium & Vitamin D
- Exercise
- Fall Prevention Planning and Fall Risk Assessment

Bisphosphonates

- Considered first line therapy for treatment or prevention
- Not absorbed very well

Generic (Brand)	Daily	Weekly	Twice Month	Monthly	Quarterly	Yearly
Alendronate (Fosamax)	10 mg oral	70 mg oral				
Risedronate (Actonel)	5 mg oral	35mg oral	75 mg oral	150 mg oral		
Ibandronate (Boneva)	2.5 mg oral			150 mg oral	3 mg IV	
Zoledronic Acid (Reclast)						5 mg IV

Osteonecrosis of the Jaw

- Occurs in patients receiving Bisposphonates
- ONJ is characterized by pain, swelling, exposed bone, infection, fracture of jawbone
- Usually occurs as a result of incomplete healing after a dental procedure
- Most cases are with high dose IV therapy

Raloxifene

- Selective Estrogen Receptor Modulator (SERM)
- Not a first line agent, only used if a bisphosphonate is not tolerated since not as effective
- Dose is 60 mg daily

Teriparatide

- A form of parathyroid hormone
- Considered to be an anabolic treatment (stimulates bone formation and remodeling)
- Black Box warning for osteosarcoma (or 300,000 patients world wide exposed, 1 case has been reported)
- Dosing is 20 mcg/day as a subcutaneous injection
- Sequential use with a bisphosphonate MAY provide greater fracture reduction efficacy

Estrogen

- Because of significant risks for breast cancer, stroke, venous thromboembolism and coronary disease, no longer considered first line treatment
- Unopposed estrogen and estrogen with progestin are highly effective at preventing hip and vertebral fractures

Rossouw JE et al, Risks and benefits of estrogen plus progestin in health postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA. 2002:288(3):321-333

Calcitonin

- A peptide that binds to osteoclasts and inhibits bone resorption
- Usually dosed as 200 IU intranasally daily
- Associated with a small reduction in vertebral fracture risk
- May have benefits for bone pain
- May also be administered as an IM or SQ injection at 100 IU ever other day

Chesnut CH, et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the Prevent Recurrence of Osteoporotic Fractures Study. Proof Study Group. AM J Med. 2000; 109(4):267-276

RANK Ligand

- Denosumab (Prolio®) [Amgen - waiting for FDA Approval)
- It is a fully-human monoclonal antibody that targets RANKL (RANK Ligand) a protein that acts to promote bone removal
- This will be the first Biologic therapy sold to primary care practitioners other than vaccines
- RANK Ligand = Receptor Activator of Nuclear Factor-Kappa B Ligand and is a member of the tumor necrosis factor receptor family
- It's action is to inhibit the actions of osteoclasts by binding to RANKL thus protecting the bone from degradation (and osteoporosis)
- Clinical trials show a 35% fracture risk reduction (comparable to Zoledronic Acid and Teriparatide and slightly more than oral Bisphonates)
- Adverse effects include urinary and respiratory infections, cataracts, constipation, rashes and joint pain.
- Dosing is a subcutaneous injection twice a year - costs are estimated to be ≈$2,000 per year

General Side Effects Associated with Common Osteoporosis Treatments

General Side Effect	Associated With:
Cardiovascular	IV Bisphosphonates, Estrogen, SERM
Esophageal Cancer	Oral Bisphosphonates
Flu-Like Symptoms	IV Bisphosphonates
Fracture	Bisphosphonates
Gastrointestinal	Bisphosphonates
Hypocalcemia/ Hypercalcemia	Bisphosphonates, Teriparatide
Musculoskeletal Pain	Bisphosphonates, Teriparatide
Ocular	Bisphosphonates
ONJ	Bisphosphonates

Non-Pharmacological Treatments

- Calcium and Vitamin D
  - Important to maintain bone health
  - Vitamin D enhances calcium absorption
  - While numerous studies demonstrate increased BMD, evidence does not support efficacy for fracture reduction
  - Several Calcium Salts are available (Carbonate and Citrate are the most common)
  - Calcium intake for postmenopausal women should be1500 mg/day
  - Vitamin D intake should be at least 800 IU/day
- Exercise
  - Weight bearing (walking, aerobics, weight training)
- Smoking Cessation

Self-Assessment Question

Self-Assessment Question

Self-Assessment Question

Self-Assessment Question

Self-Assessment Question

Questions and Discussion

Self-Assessment Questions
Answer Key:
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