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OSTEOPOROSIS, WHAT IS NEXT FOR THE NEW DECADE?

DEFINITION:

1. Osteoporosis is the most common Metabolic Bone Disease which leads to a greater likelihood of fracture.

   The World Health Organization has defined osteoporosis based on a patient's bone density measurement.

   Normal bone density; T score is between +1 and -1.
   Low bone density (osteopenia) T score is between -1 and -2.5.
   Osteoporosis is less than T score of -2.5.

   Bone density testing is the most accurate way to determine a patient's risk for fracture. Guidelines for testing have been established and yet less than 11% of all postmenopausal women who meet the criteria have had a DEXA. The vast majority of patients discharged from a hospital with a diagnosis of major fracture will not have had a DEXA a year after.

   The current reimbursement for this important diagnostic study is in peril. The consequences are that fewer patients are now being tested and there is concern that in the future we may start to see a rise in the fracture rates that had once begun to fall.

   We should contact our legislators who are actively reviewing the status of reimbursement by either writing to them or going on the websites of the International Clinical Society for Densitometry; http://www.iscd.org or the National Osteoporosis Foundation; http://nof.org.

2. Risk Factor Assessment

   As with any important clinical illness, in osteoporosis we evaluate the patient's medical history and those associated clinical risk factors which are most strongly associated with fracture.

   The following is a list of some of the more common associated risk factors.

   1. Small frame, Caucasian and Asian female
   2. Family history of fracture
   3. Postmenopausal female
   4. Early surgical menopause

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5. High doses of Synthroid or low doses of Prednisone, 5 mg. daily for more than 3 months
6. Cigarette smoker or excess alcohol use
7. Vitamin D deficiency

Secondary causes should be investigated in patients with very low bone mass or those not responding to medical therapy such as gastrointestinal disorders like Inflammatory Bowel Disease and Celiac Disease.

Additional issues to consider are medications other than corticosteroids, such as Dilantin; aromatase inhibitors; heparin; and the class of diabetic medications, thiazolidinediones.

3. What is a FRAX Measurement?

A FRAX measurement is a calculation that predicts an individual's likelihood of having a major osteoporotic or hip fracture in the next 10 years. This measurement is based on a patient's clinical risk factors for fracture and a patient's bone density T score at the femoral neck. This algorithm has been extensively studied worldwide and the calculation of this measurement has been determined in different countries for different demographic groups.

Some limitations to the FRAX are that it has not been validated in patients already taking medications and for those patients who might have severe bone loss at the spine but mild bone loss at the hip. Thus the FRAX score may be normal.

A value for the hip site is 3 or less and for other sites is a score of 20 or less.

The FRAX allows the physician and patient to better strategize a treatment plan that will assess the need for medical therapy when taking into account a patient's long term risk of a fracture.

4. Oral vs. Intravenous Therapies

The primary class of anti-resorptive therapies that are used to treat osteoporosis are the bisphosphonates. These are a potent group of medications that slow bone loss by primarily impairing osteoclast formation. There have been numerous clinical trials which demonstrate that these oral medications can quickly reduce fracture rates at both the spine and the hip.

Some have been shown to be more effective at both sites than others but this has often been a result of the study design.

Significant limitation of taking oral bisphosphonates is that they are poorly absorbed and they need to be taken only with water in the early morning. Additionally, there needs to be a delay of approximately one hour before a patient can eat. A major challenge to their use has been patient's adherence and compliance. Many studies demonstrate after 6-9 months of taking a weekly or monthly oral bisphosphonate 70% of patients will discontinue therapy. Patients can easily get frustrated or forgetful, even those who may have had a fracture in the past year. Physicians may not be as motivated to encourage their patients to continue with the therapy. With complex medical patients who have heart, lung and kidney diseases 'the bones' sometimes are not prioritized.

Thus, there is an advantage to annual intravenous bisphosphonate therapy. There appears to be improved fracture results at the hip with the use of yearly Zoledronic Acid .

All patients should be taking Calcium and Vitamin D by diet and or supplementation. Most do require some additional supplements particularly Vitamin D 3 in amounts between 1000-3000 units daily. The target level for 25 OH D should be at least 30 ng/ml.

Estrogen is a hormone therapy available for treatment of osteoporosis.

Estrogen,[ET] and hormone replacement ,[HT] as primary treatment for osteoporosis is controversial. The findings of the Women's Health Initiative in 2001 has changed how many physicians prescribe ET. The results showed an increase in breast cancer and cardiovascular events who took ET. There was a definite reduction in fractures regardless of the use of progesterone. Contraindications to the use of ET include the following: thrombophlebitis, a history of active hepatitis and they should be used carefully in patients with Lupus. Most physicians recommend using ET/HT at the lowest dose for the shortest period of time.

Selective Estrogen Receptor Modulator[SERM]

SERMs represent a special family of estrogen compounds .These new 'designer' drugs activate certain tissues by their effect on estrogen receptors. This family has the good benefits of ET on bone without some of the negative effects on endometrial stimulation and breast cancer.

Examples of SERMs include Tamoxifen ® that is used to treat breast cancer. Evista ® is used in the prevention and treatment of osteoporosis. In 2007, Evista® was approved by the FDA for the prevention of breast cancer in two groups of women. The first is postmenopausal women with osteoporosis and the second are those postmenopausal women at a high risk for invasive breast cancer.

Calcitonin

Calcitonin's action is to also inhibit osteoclasts and thus can reduce bone loss. The fracture data is not as potent as that of the BP and so they are not used as often and relegated to a second tier of treatment. Examples include Miacalcin and Fortical ®.

5. Osteonecrosis of the Jaw (ONJ)

During the past several years there has been a growing recognition of osteonecrosis of the jaw reported with all bisphosphonates and in 2007 a package labeling change was included for this class of medications.

The first reports were initially observed in patients who were treated with high doses of bisphosphonate therapy for oncologic tumors including breast cancer that had metastasized to bone and multiple myeloma.

Much research has looked at the possible causes which include:

A. Decreased resistance because of the use of immunosuppressive and cytotoxic medications.

B. The use of corticosteroids and increased oral infection and systemic bone resorption.

C. Shortly after, there are less well documented cases reported in both the medical and non-medical journals implicating Fosamax as a possible cause of osteonecrosis in postmenopausal osteoporosis.

Since that time there have been several well-studied reports attempting to document the true prevalence of this condition. The American Society for Bone Mineral Research, along with many other professional organizations, has established guidelines for monitoring and treating patients who may be having complex dental procedures. Usually, patients will stop their

bisphosphonate at least 3-6 months prior to and after the procedure depending upon its complexity.

Overall the safety of this class of medications has been well established in postmenopausal osteoporosis. From the following studies that have been observed in Europe, the United States and Canada the true prevalence of ONJ in postmenopausal osteoporosis appears to approach 1 in 100,000 patients. While in patients who might have an underlying malignancy the number is 2 in 100,000.

6. Subtrochanteric and Atypical Fractures in Postmenopausal Women

The long term safety of bisphosphonates has been well established with bone biopsies and clinical data. However, there are a few series and some case studies reporting the possible association of prolonged use of bisphosphonate, usually Alendronate, with the onset of a low energy femoral fracture.

They found women who had used Alendronate for several years had a unique
x-ray pattern with cortical thickening. Some had contralateral x-ray changes also and were thought to be at high risk to fracture the other femur.

The mechanism of action is uncertain but may be related to the prolonged incorporation of bisphosphonates into bone and suppression of bone turnover.

The prevalence of this is quite uncommon. It is difficult to identify these patients prior to their fracture based on symptoms and it is prudent to realize that bisphosphonate use has decreased the risk of hip fractures 15 fold.

7. New Medications

A. Anabolic Medications:

Teriparatide: This is a recombinant human parathyroid hormone [I-34]. The compound is unique because it stimulates the osteoblast, the bone forming cell and has been shown to make both new cortical and trabecular bone. Teriparatide was FDA approved in 2002 and is indicated for postmenopausal women and men at high risk for fracture and for those patients with corticosteroid associated bone loss. Teriparatide is self administered

subcutaneously once daily in a pre-filled syringe for two years and then followed by continuing on a bisphosphonate to maintain and increase BMD.

A very small risk of osteosarcoma was observed related to the medication in pre-clinical trials in rats when given 3-60 times the treatment dose. The prevalence of osteosarcoma in the general population is about 4 cases per million. More than 1.5 million patients have received the drug since its approval. There is an active ongoing registry to determine the number of cases that may occur while patients are on the drug. Patients who have had cancer and have received radiation therapy should not receive Forteo as well as patients who have documented primary hyperparathyroidism.

B. New therapies:

Anti-Sclerostin antibody: This molecule is actively being studied in pre-clinical and clinical trials. Its discovery came about from research of a rare disease, sclerostenosis, in which a mutation has occurred causing very hard dense bone.

Animal studies have shown that the quality and density of the bone is very sturdy. Sclerostin is produced primarily in the osteocyte making this a novel location to study bone activity.

Strontium Ranelate: This heavy metal has been actively studied for the treatment of bone loss for more than twenty years. It appears to both stimulate the osteoblast and also have an opposing effect on the osteoclast, what some have referred to as the 'Holy Grail' of treatment. Numerous trials have been performed which have shown good spinal fracture efficacy. The medication is manufactured in France by Servier as an oral tablet and is approved and used in many countries including England. There has been doubt and concern raised in the USA with regards to safety and thus far approval is dubious.

Denosumab : This compound blocks Rank ligand an important cytokine that controls osteoclastogenesis, thus allowing more bone to be formed. The compound is administered subcutaneously twice yearly. The large body of phase 3 trials have demonstrated that there is not only good fracture reduction at the spine comparable to those with the bisphosphonates but a fracture reduction of about 40% at the hip similar to what had been reported with Zoledronic Acid .Denosumab was approved last year for post menopausal osteoporosis .

Odanacatib: This compound blocks Cathepsin K which is expressed in osteoclasts and is the predominant cysteine protease in these cells. This is

an integral compound which breaks down the protein matrix of bone. By deleting the Cathepsin K gene in mice this has been shown to cause osteopetrosis. This is a hereditary condition referred to as marble bone because of the appearance of very dense bone. However the bone is actually more susceptible to fracture because of this imbalance of bone structure.

Merck has just completed phase 2B clinical trials with this drug showing positive gains in BMD at the spine after 3 years with modest gains at the hip. Large phase 3 trials are now ongoing to determine fracture effects at the spine, hip and non-vertebral sites.

PTH-34 Analogs: New formulations of PTH I-34 are in development. Zelos Pharmaceuticals has ZT-034, which is being studied for the treatment of postmenopausal osteoporosis. In addition to a once daily subcutaneous injection, a nasal preparation is being evaluated.

PTH and PTHrP ligands: Both of these molecules stimulate new bone through their action on the PTH/PTHrP receptor [PTHR 1]. This family of anabolic compounds would be good candidates. Ideally they would be small oral agents with limited exposure time on the receptor thus the risk of hypercalcemia would be reduced. The structural properties of the receptor and the signaling mechanisms are very complex and have not been completely identified. Thus far no therapeutic drugs have been developed.

8. Summary

This new decade offers many challenges with regards to diagnosis, patient assessment and treatment. We have many new and improved therapies to reduce fracture. The tool chest of new therapies also looks promising. We should be hopeful and optimistic that many of the serious complications of osteoporosis including spinal deformity, gait and posture disturbances and of course fracture can be limited.

The continuing challenge is to recognize the HIGH RISK patient before the FIRST FRACTURE and to encourage and MOTIVATE them to stay on their medical therapy.

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