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Osteoporosis and Bone Health

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Abstract: Osteoporosis is a metabolic bone disorder, which is characterized by a decreased in the overall amount of bone mass. This is major public problem with 30% mortality rate within the first year following osteoporotic hip fracture. The altered microarchitectural structure of bone would lead to increased susceptibility to fractures. By improving the public health and aging of the population, the incidence of this disorder is also increasing. Different treatments costs of patients is showing an increasing trend, which implies that there should be a public education regarding this threatening abnormality. Prevention rather than treatment has to be publicized by correct instructing the population and especially in the women society. This review has a brief simple but concise outlook at osteoporosis its manifestation, treatment and prevention.

Key words: Osteoporosis, menopause, estrogen, bone mass, fracture, bone healing

INTRODUCTION

Osteoporosis: Osteoporosis is a heterogeneous cluster of abnormal processes characterized by the net loss of bone, that results in a decrease in total mineralized bone without a decrease in the ratio of bone mineral to the organic matrix (Simon, 2005; Riggs and Melton, 1983, 1986; Melton and Riggs, 1989; Nagant, 1983; Parfitt *et al*., 1992). As the result, there is a decrease in the overall amount of bone. By histopathologic analysis, the size of the osteoid seam is normal but there is a decrease in the thickness of the cortex of cortical bone and as well a decrease in the number and size of the trabeculae in cancellous bone. The trabecular plates have increased perforations and there is a decrease in trabecular connectivity (Parfitt *et al*., 1992, 1983, Riggs and Melton, 1992; Parfitt, 1988). Trabecular connectivity is probably an important determinant of the level that bone may be compressible and thus, absorb energy suggesting that connectivity is an important determinant of the tensile strength of bone. Eventually, osteoporosis would lead to bone with less tensile strength and significantly more susceptibility to fracture with less force.

At some points, the amount of bone available for mechanical support drops below a certain threshold and the patient may sustain a fracture. It should be noted that there is no absolute fracture threshold for a population of patients however, it is different in each individual. The bone loss affects both cortical and trabecular bone with trabecular bone loss more predominant in postmenopausal osteoporosis (Simon, 2005).

MATERIALS AND METHODS

Pathophysiology: In human peak bone mass is achieved by an individual in the middle of the third decade of life. After a plateau period of about 5 years, during that there is a steady turnover of bone formation equal to bone resorption, there begins a period of net bone loss equivalent to about 0.3-0.5% annually. When menopause occurs women sustain an accelerated phase of bone loss, which may increase 10-fold, so that for approximately 5-7 years they may lose bone at the rate of 3-5% per year (Simon, 2005; Riggs and Melton, 1983, 1986; Melton and Riggs, 1989; Nagant, 1983; Parfitt *et al*., 1992). As the obvious fact, accelerated bone loss is the dominant effect in postmenopausal osteoporosis. The reason is the osteoblastic and osteoclastic activities are controlled by systemic hormones and cytokines such as Parathyroid Hormone (PTH), calcitonin, estrogen and 1-25-dihydr-oxyvitamin D3 (Lukert and Raisz, 1990; Manolagas and Jilka, 1995) and estrogen deficiency is a major cause of accelerated bone loss (Simon, 2005; Jilka *et al*., 1992; Passeri *et al*., 1992; Lukert and Raisz, 1990;

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Manolagas and Jilka, 1995). Estrogen deficiency is shown to affect circulating levels of some cytokines such as IL-1, Tumor Necrosis Factor-a (TNF-a), Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) and IL-6 (Manolagas and Jilka, 1995). With the progressive diminish of estrogen, levels of these cytokines rise and augment bone resorption by increasing the recruitment, differentiation and activation of osteoclast cells (Kloen *et al*., 1992). The increased activity of cytokines lead to the generation of transcription factors which consequently leads to increased osteoclastic recruitment and development. The mediator of this activity is RANKL, generated from osteoblasts and other cells including the immune system leading to increased bone resorption.

Some other factors as well affect the bone mass (Riggs and Melton, 1983, 1986; Melton and Riggs, 1989; Melton *et al*., 1986; Finklestein *et al*., 1992; Cummings, 1985). Physical activities would increase bone mass while, immobilization will increase bone loss. Obesity is associated with higher bone mass. Typical patients with osteoporosis are thinner and possess lesser muscle mass (Daniell, 1976; Seeman *et al*., 1983). Low dietary intake of calcium, phosphorous and vitamin D are associated with bone loss however, it is more obvious in higher ages after passing the plateau period. The body's acid-base balance is also important for example, the alkalization of the blood with bicarbonate has been shown to retard bone loss. Sex also influences the bone mass, men have higher bone mass than women (Simon, 2005; Seeman *et al*., 1983). Genetic factors are the most significant determinant in defining an increased risk of the development of osteoporosis (Christian *et al*., 1989).

Specific abnormalities in genetic and hormonal factors appear to be important to define two clinical subtypes of osteoporosis (Melton *et al*., 1986). Type I osteoporosis occurs in hypogonadal individuals. Postmenopausal women and also men after castration or associated with testosterone deficiencies would develop bone loss that is directly related to the loss of gonadal functions (Finklestein *et al*., 1992). As mentioned earlier, loss of estrogen will due to increased blood levels of cytokines, which is shown to lead to increased employment and responsiveness of osteoclast precursors in trabecular bone, resulting in increased bone resorption (Manolagas and Jilka, 1995). As a result, these patients present with fractures of the skeleton, where trabecular bone is predominant, such as the distal forearm or vertebral bodies. Type II osteoporosis on the other hand, is associated with the normal aging process and is seen in any individual in higher ages (Melton *et al*., 1986). Aging is associated with a progressive decline in the amount of osteoblasts as well as a decrease in their activity but not with an increased in osteoclastic activity (Riggs and Melton, 1992; Parfitt, 1988; Parfitt *et al*., 1983). However, this subtype also leads to net loss of bone but now because of a decreased in formation and not due to increased resorption. Fracture of cortical bones, such as in the femur, femoral neck, proximal tibia and pelvis are more common in this group. Other pathological circumstances also can lead to abnormalities of bone metabolism that increases the risks of bone loss including either the individuals with increased endogenous production of glucocorticoids or those with inflammatory diseases that are treated with exogenous glucocorticoids. The pathogenesis of glucocorticoid-induced osteoporosis is very complex, but is obvious that it is because of several induced abnormalities such as changes in gonadal hormone secretion, decrease in calcium absorption and increase urinary calcium excretion as well as the direct effects of glucocorticoids on bone cells (Ramos-Remus *et al*., 1992; Nagant, 1983; Baylink, 1983). Glucocorticoids have been shown to reduce pituitary gonadotrophin secretion and suppress adrenal androgen production. These potent anti-inflammatory drugs also decrease intestinal calcium absorption even with normal serum levels of calcitriol. Besides, the other skeletal effects of glucocorticoids include inhibition of osteoblast function increased sensitivity of the cells to the effects of parathyroid hormone and also transiently increased osteoclast activity (Simon, 2005).

Glucocorticoids also inhibit the generation of osteoprotegerin, a factor that inhibits RANK ligand. RANKL (Receptor Activator for Nuclear Factor κ B Ligand) also known as TNF-related activation-induced cytokine (TRANCE), Osteoprotegerin Ligand (OPGL) and ODF (Osteoclast Differentiation Factor) is a molecule important in bone metabolism. This natural and necessary surface-bound molecule activates osteoclasts, cells involved in bone resorption (Wikipedia.com).Thus, by decreasing inhibition of the inhibitor for RANK ligand there is increased a huge production of osteoclastic precursors and the generation of more osteoclasts. Bone loss with glucocorticoid therapy is most significant in trabecular bone and is closely related to the dose and duration of glucocorticoid therapy and can be rapid. A significant amount of this bone loss is owing to glucocorticoid-induced secondary changes in calcium balance (Hahn *et al*., 1979; Buckley *et al*., 1997). Another important factor is the quality of bone. Bone's quality reflects the extent of its connectivity and is very important component of bone strength in facing with osteoporosis-inducing factors (Simon, 2005).

RESULTS AND DISCUSSION

Differential diagnosis: Osteoporosis can occur as a primary disorder or secondary as a disorder associated

with other diseases. Primary osteoporosis is a disease of aging. This form of osteoporosis is sometimes referred to as involutional osteoporosis. Secondary osteoporosis is a series of abnormalities and diseases that would manifest with effects on bone. Those diseases are associated with osteoporosis induction and include endocrine disorders, systemic inflammatory diseases, bone mineral and metabolic defects and some other chronic illnesses. Some endocrine diseases that affect bone include hyperthyroidism, hyperadrenocortism (Cushing's disease) and hyperparathyroidism. Systemic inflammatory diseases that will induce osteoporosis include inflammatory bowel disease, rheumatoid arthritis and systemic lupus erythematosus (Melton and Riggs, 1989; Melton *et al*., 1987). Osteoporosis may also result from therapeutic interventions, some examples include methotrexate drug therapy (decreased osteoblast function) heparin (increased osteoclast activity), glucocorticoids or the use of anticonvulsants (which effect vitamin D metabolism and calcium absorption) (Hahn *et al*., 1979). Other diseases commonly associated with an increased incidence of osteoporosis include diabetes mellitus and chronic obstructive pulmonary disease (Daniell, 1976; Seeman *et al*., 1983; Hahn *et al*., 1979; Simon, 2005).

Clinical manifestations: The clinical features of osteoporosis are bone lesser quality, weakness, fracture, pain and deformity. Pain is the most common of symptoms. The axial skeleton is the most commonly involved area with fractures occurring frequently in the mid thoracic, lower thoracic and lumbar spine vertebrae. Spontaneous high thoracic or cervical fractures associated with minimal or no trauma should raise the suspicion of a malignancy. Osteoporotic fractures are typically sudden in onset and may be caused by a fall, sudden movement, lifting, jumping or even without any evidence of traumatic events such as a cough. Pain may be severe and typically localized to the site of fracture but can radiate to the abdomen or flanks. However, bone pain is not the sign of osteoporosis only generalized bone pain is rare and should raise the possibility of other diseases, such as metastatic cancer or osteomalacia (Simon, 2005).

Most patients with an osteoporosis related fracture sustain further fractures within the first few years (Cumming, 1985; Metlon *et al*., 1986). Femoral neck fractures occur mainly in aged individual and increase in incidence as patient age (Riggs and Melton, 1983; Melton and Riggs, 1989). Once a patient fractures a hip, there is a significant increased risk of death within 1 year (Cumming, 1985). This increased mortality is typically the result of complications of the fracture or reparative surgery however, hip fractures are often sustained by patients who are chronically debilitated for other reasons. Physical examination reveals sensitivity to palpation over the fractured area, spinal deformity, loss of height and over time development of a lax abdominal musculature with a protuberant abdomen. Progressive vertebral compression induces a severe kyphosis of the thoracic spine, which due to a characteristic deformity called a dowager's hump (Simon, 2005).

Laboratory and radiologic findings: Histopathology is the gold standard technique to determine the state of bone turnover and diagnosing disease unfortunately, the method is invasive requiring transiliac bone biopsies obtained with a trefine that has an internal diameter of 7-8 mm (Vedi *et al*., 1982). Although, it is a technique providing an enormous amount of information, it is not commonly used in clinical practice because of its invasiveness.

There are also some newer methods to extent of bone turnover without relying on radiocalcium kinetics or direct measurement by bone biopsy. Biochemical markers can be measured in blood or urine, which define either markers of osteoblastic or osteoclastic function the amount of new collagen or noncollagenous proteins synthesized the extent of activity of osteoblasts or the amount of bone collagen that has been resorbed (Taylor *et al*., 1994). The degree of elevation of indices of resorption and formation reflects the extent or severity of the abnormal bone turnover. Unfortunately, these markers of bone turnover have not yet been determined to reflect bone mass, quality of bone or predict risk for fracture alone. The biochemical markers for new bone synthesis are serum alkaline phosphatase, bone specific alkaline phosphatase, type I procollagen carboxyterminal peptide and osteocalcin (Eriksen *et al*., 1993; Kushida *et al*., 1995; Simon *et al*., 1984). As a result of bone resorption, several of the collagen breakdown products are excreted in the urine. These include peptides containing hydroxyproline, hydroxylysine and glycosylated hydroxylysine that are present in all type I collagens of all sources or the 3hydroxy-pyridinium cross-link compounds that are unique to bone type I collagen (Eriksen *et al*., 1993; Kushida *et al*., 1995; Taylor *et al*., 1994).

Elevated blood levels of serum alkaline phosphatase activity indicate increased activity of the osteoblasts (Panigrahi *et al*., 1994). The bone specific serum alkaline phosphatase assays have not yet been proven to add more information except in patients with concomitant liver disease (Panigrahi *et al*., 1994; Simon, 2005). Another common blood factor for bone synthesis includes serum osteocalcin measurements. Osteocalcin signify about 20%

of the noncollagenous component of the organic bone matrix and undergoes variable processing that can lead to multiple possible immunoreactive peptides circulating in serum, which might intensely confound the results of some assays. It is known to be a indicator associated with osteoblast function is deposited within the matrix and thus may be variably released with resorption. There is some evidence that it might also be associated with the process of mineralization. Serum levels of the type I procollagen carboxyterminal is another marker of new synthes (Simon, 2005).

The urinary indicators of resorption or osteoclast activity are hydroxyproline-containing peptides or pyridinium cross-linked peptides, which serve as rapid predictors of changes in osteoclastic activity. The newer pyridinium cross-link markers are predominantly related to bone collagen resorption particularly in active disease states (Taylor *et al*., 1994). Some studies suggesting the patients with high levels of the urinary markers for bone resorption have lower bone densities as determined by densitometry. Low bone mass is associated with an increased risk for fracture (Simon, 2005).

Skeletal mass measurements: Radiologic measurements allow the definition of skeletal architecture. However, the typical radiograph reveals only a semiquantitative assessment of skeletal mass (Singh *et al*., 1972). In specific epidemiologic studies, the cortex of a specific bone is precisely measured using radiogrametry (Meema and Meema, 1969). Although, inexpensive, non invasive and available this technique provides little information about trebecular bone, which is the most metabolically active and is the area of bone most involved in postmenopausal osteoporosis. Some methods have been developed for quantization of cortical and trabecular bone mass as well as potential risk for fracture (Bergot *et al*., 1988; Kelly *et al*., 1988).

Single-Photon Densitometry (SPD), Dual-Photon Absorptiometry (DPA), Dual energy X-ray Absorptiometry (DXA) and Quantitative Computed Tomography (QCT) are being used to accurately and reproducibly assess the mineral content of the skeletal bone (Simon, 2005).

Diagnosis: The diagnosis of osteoporosis in postmenopausal or aged individuals, who presents with pain and a vertebral compression fracture is uncomplicated. As noted, radiograph changes are insensitive to early changes of osteoporosis and clinical symptoms of pain are typically lacking. Additionally, there are no specific laboratory abnormalities associated only with osteoporosis. The serum calcium, phosphate and alkaline phosphatase are usually normal for age and sex. There may be hypercalciuria and elevated urinary hydroxyproline or hydroxypyridinium excretion but not always these finding accompany osteoporosis (Simon, 2005). However, in patients without any constant pain and pathologic fracture, diagnosis is a very though job.

Before the diagnosis of osteoporosis is assigned to a patient with risk factors for osteoporosis or a screening radiograph consistent with osteoporosis, it is prudent to exclude other diseases that are associated with osteoporosis. Elevated serum calcium suggests either carcinomatous skeletal metastases or hyperparat-hyroidism hence, it is not a constant and definite osteoporosis indicators. Other markers indicating of the status of liver and kidney as well as hematological parameters should be checked. Once osteoporosis is completely differentiated with its associated disorders only then it should be assigned to the patient.

Management: The fundamental management goals for patients with osteoporosis are to prevent fractures, decrease pain and maintain function. Some available drugs decrease the risk for further bone loss and reduce the risk of bone fracture.

The first step to choose the appropriate medication is the precise diagnosis. Diagnosing patients with pain resulting from a vertebral compression or femoral fracture is not such complicated. The goal is to diagnose the patient with osteoporosis before they are undergone bone loss to be at risk for a fracture.

Once a patient got an osteoporotic fractured, therapeutic interventions are focalized to decrease pain by pharmacologic interventions such as analgesics, nonsteroidal anti-inflammatory drugs, muscle relaxants or even the use of calcitonin for its acute analgesic effects (Simon, 2005).

The pharmacologic treatment strategies for the prevention and treatment of type I and type II osteoporosis include medications that decrease osteoclast-induced bone resorption. Even in age-related osteoporosis where new bone formation is decreased since accelerating osteblastic activity is harder to achieve hence, in those cases also osteoclastic resorption should be ceases by drug therapy. Antiresorptive drugs include calcium and vitamin D supplementation, Hormone Replacement Therapy (HRT), such as estrogen supplementation, calcitonin and bisphosphonate therapy. Medications aiming in stimulating osteoblasts and new bone formation include sodium fluoride, androgens and intermittent parenteral parathyroid hormone therapy. Because type II osteoporosis is related to decrease osteoblastic activity, drugs to stimulate osteoblast function would be preferable. Unfortunately, there are significant problems with several of the anabolic therapies including the potential for virulization and hepatic toxicity

because of androgens or the potential for increased bone pain or the development of bone of poor quality associated with fluoride treatment. PTH treatment has been shown to be successful (Buckley *et al*., 1997; Simon, 2005).

Treatment and prevention

Calcium, vitamin D: Calcium supplementation of the normal diet increases bone mass in adolescents and reduces bone loss associated with advancing age (Buckley *et al*., 1997). Relative vitamin D deficiency, like calcium deficiency is a problem in postmenopausal individuals. Some studies have shown that vitamin D3 plus calcium appears to reduce the risk of hip and other nonvertebral fractures by as much as 43% in elderly ages (Chapuy *et al*., 1992).

Estrogen: Estrogen deficiency is now well established as a major cause of bone loss in postmenopausal individuals (Richelson *et al*., 1984). Estrogen replacement therapy is associated with increased bone mass decreased urinary biochemical resorption markers and reduced fracture rate in many studies (Felson *et al*., 1993; Lafferty and Fiske, 1994). Estrogen replacement appears to be most effective at maintaining bone mass, when begun soon after menopause and continued. This is due to the accelerated period of bone loss during the early period of postmenopause. Side effects of treatment with estrogen include uterine and breast cancer (Colditz *et al*., 1990; Berkvist *et al*., 1989).

Calcitonin: Calcitonin inhibits bone resorption by decreasing osteoclast function by binding to high-affinity receptors (Mazzuoli *et al*., 1986). Common side effects of calcitonin therapy included nausea and flushing. Calcitonin therapy is also hampered by cost and the inconvenience of injections. Also, nasal calcitonin is not so effective in peripheral skeleton (Overgaard, 1994; Overgaard *et al*., 1989).

Bisphosphonates: Bisphosphonates are synthetic analogs of pyrophosphate, a naturally occurring substance that inhibits bone mineralization. The bisphosphonates have been shown to inhibit bone resorption by inhibiting the action of osteoclasts (Geusens *et al*., 1992).

Sodium fluoride: Sodium fluoride therapy increases trabecular bone mass, but may at the same time decrease cortical bone mass even in the presence of adequate calcium supplementation (Riggs and Melton, 1986). Though patients receiving sodium fluoride might improve bone mass with a lower dose confirmation of a benefit from sodium fluoride is lacking.

Parathyroid hormone: Conventional therapies for osteoporosis have been goaled in inhibiting of bone resorption. Therapies that intended increased osteoblast activity replacing lost bone by increasing new bone formation are now available, parathyroid hormone therapy have been considered for years (Simon, 2005).

Androgens: Since androgen deficiency tends to plays a role in age-associated bone loss, androgen replacement shown to stimulate osteoblasts to produce new bone. Androgens have been shown to decrease urinary calcium excretion, increase muscle mass and perhaps provide an improved sense of well-being. Stanozolol and nandrolone augment bone mass in postmenopausal patients (Simon, 2005). The male patient with osteoporosis presents a unique problem (Simon, 2005). If the patient is hypogonadal, the use of testosterone by injection or patch is appropriate (American College of Rheumatology Task Force on Osteoporosis Guidelines, 1996).

Strontium ranelate: As a new agent, strontium ranelate, with mechanism acting on bone resorption also on bone formation to promote the growth of new bone has recently been heralded for osteoporosis treatment (Meunier *et al*., 2004; Compston, 2004).

Osteoporotic fracture: As discussed within this research, osteoporotic fracture is a challenging issue. Since, osteoblastic activity is minimal and osteoclasts are resorpting bone to accelerate the osteoporotic bone fracture healing, patients should be received the implants with very high potential to form new bone aiding bone healing on its best fashion.

CONCLUSION

Consequently, the study concerned found that the Use of osteogenic, inductive and conductive implants simultaneously would boost and accelerate the rate of new bone formation and bone healing. Bone Tissue Engineering (BTE) approaches has been heralded in this way but still studies one osteoporotic bone fracture and pathologic bone healing patterns are so scant and requires more efforts to find out the best BTE approach in such patients.

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