Abstract

Osteoporosis (OP) is a generalized skeletal disorder characterized by low bone mineral density (BMD), deterioration of the microarchitecture of bone tissue and susceptibility to fracture. Most frequently it occurs in postmenopausal women and the aged. It is a chronic condition of multifactorial etiology and is a major global healthcare problem in developed and rising in developing countries. Patients with uncomplicated OP are usually asymptomatic which contributes to serious underdiagnosing of this potentially devastating condition. It is estimated that less than half of patients with OP are diagnosed in many developed countries. Therefore preventive measures and timely diagnosis have to be a key aspect of management of this disorder. In this article we briefly underline patophysiology of the disorder, review current methods of measuring bone mineral density, describe risk factors and evaluate current and potential therapies.

KEY WORDS: osteoporosis, bone mineral density, pharmacotherapy

Introduction

Osteoporosis can be divides into 2 main types primary, which is usually subdivided in type 1, or postmenopausal, and type 2, or senile, and secondary, where the bone loss is caused by underlying condition such as chronic medication (steroids), malignancy, endocrine, renal, gastrointestinal and other systemic diseases. It is estimated that at least 20% of women have suffered one or more fractures (vertebral, hip or wrist) by age 65 and as many as 40% have fractures thereafter. As many as 20-30% of older with hip fracture die of cardiopulmonary problems, while 50% of those who survive become dependent on nursing home care (1, 2). The number of hip fractures worldwide due to OP is expected to rise enormously, almost
In the past diagnosis of osteoporosis was made based on a fragility fracture but now we have bone density tests and many options for prevention of osteoporotic fractures. In 1994, the World Health Organization (WHO) proposed a clinical definition of osteoporosis based on measurement of bone mineral density (BMD). According to it, a patient is osteoporotic if BMD shows 2.5 standard deviations (SDs) below typical peak bone mass of young healthy adults for the sex and race of the patient. This measurement of standard deviation from peak mass is called the T score. Osteopenia has been defined as a BMD of -1.0 to -2.5 (1).

Bone is an active metabolic tissue and is constantly being formed by the osteoblasts and resorbed by osteoclasts. About 10% of bone is replaced each year, so that the entire skeleton turns over every 10 years. This metabolic activity occurs throughout the different types of bone tissues, the cortical and cancellous. The sites of metabolic activities vary in their sensitivity to hormonal action. Estrogens are active in bone formation in men as well as women. Androgens stimulate periosteal bone formation, while estrogens stimulate more endosteal bone formation. Estrogens not only increase bone formation, they inhibit bone resorption by decreasing the activity of osteoclasts. With low estrogen bone resorption increases and the actual mechanism is a decrease in the inhibition of osteoclast formation, resulting in bone loss. In women, this occurs at the time of menopause. Recent evidence suggests that estrogen deficiency makes bone more sensitive to the effect of parathyroid hormone (PTH), leading to an increase in calcium (Ca) release from bone, a decrease in renal Ca excretion and increased production of 1,25-dihydroxyvitamin D (1,25(OH)₂D₃). Increased production of 1,25(OH)₂D₃ in turn, increase Ca absorption from the gut, increase Ca resorption from bone, and increase renal tubular Ca resorption. PTH secretion then decreases by a negative feedback effect, causing the opposite effects (4). In the first 5-8 years of menopause, 1%-2% of bone is lost per year in addition to the 0.4% of bone lost per year after peak bone density is achieved at age 25-30. In men, age-related decreases in estrogen also result in increased bone resorption (4). With the lack of estrogen, more precursor cells in the bone marrow differentiate into osteoclasts. Research on osteoclast inhibition has now led to the discovery of the osteoclast differentiation factor, called receptor activator of nuclear factor-kappa B ligand, or RANKL. This ligand is the common factor for all mediators of osteoclast formation. Compounds that inhibit RANKL would decrease osteoclast formation and direct the metabolic balance toward bone formation, opening new opportunities for treatment (2).

**DIAGNOSTIC EVALUATION AND RISK FACTORS**

**MEASURING BONE MASS**

Measurement of bone mineral density (BMD) is used as a surrogate for bone mass, which indicates the amount of bone in the whole body or in a specified area of bone. BMD testing is the best predictor of fracture risk. The techniques mostly used include single and dual-energy x-ray absorptiometry (SXA and DEXA), quantitative computed tomography (QCT) and quantitative ultrasound (5). Currently DEXA is the most precise and recommended method for BMD measurement. It is a sensitive technique and can detect small changes in bone mass by comparing the patients bone density to that of healthy (T score) and to age-matched adults (Z score). In DEXA, bone mineral density is expressed as the mineral content divided by a given area of bone in two dimensions. The sites usually measured are the hip and lumbar vertebrae but heel and distal radius are also used. DXA is currently the test used most commonly for diagnosis and treatment decisions for OP. QCT measures density in three dimensions and can give a more accurate picture of trabecular bone density. The radiation exposure is much higher than DEXA and its value in clinical practice has not been determined. Ultrasound can determine bone density based on the transmission of sound waves through bone. This has been used on the calcaneus as a screening test. There is more variation in the results compared to DEXA. They are best used for screening and referral for definitive diagnosis and treatment if indicated (6). Conditions like hyperthyroidism, hyperparathyroidism, Cushing’s disease, hypogonadism and many others, can cause OP, secondary one, but routine screening for these conditions is probably not cost effective. In this situations it is more useful to look at the BMD compared to the age group, the Z score rather than the T score. A Z score of -2 to -3 may indicate an underlying medical illness or effect of chronic medication that should be detected. The underlying condition must adequately be treated in order to insure success with specific treatment for OP (6).

**RECOMMENDATIONS AND RISK FACTORS**

According to the U.S Preventive Services Task Force guidelines all women over age 65 should be screened for...
The risk factors to be considered are low body weight, weight loss, family history, smoking, alcohol or caffeine use, low calcium and vitamin D intake (1,7). The National Osteoporosis Foundation also recommends screening postmenopausal women who have had a fracture (8). Currently clinicians have been widely criticized for not following these guidelines and adequately treating patients, both men and women found to have OP. Therefore, careful medical history and physical exam should be performed in order to detect high risk patients for development of the disorder (9). Medical history and physical exam should include data on: vertebral deformity, wrist or other fracture not due to major trauma in a postmenopausal patient; previous surgeries (hysterectomy, oophorectomy, gastrectomy); family history; habits such as cigarette smoking, alcohol consumption and caffeine use; level of physical exercise; dietary habit regarding calcium and vitamin D intake and eating disorder; medications: corticosteroids, anticonvulsants, heparin, cyclosporine, aromatase inhibitors, chemotherapy (1,2). Low body weight is positively associated with OP. Weight of less than 60 kg has a positive likelihood ratio (LR+) for OP of 3.6, while weight less than 52 kg carries an LR+ of 7.3 (9). Obesity appears to protect skeleton in several ways: by increased production of estrone in fatty tissue, by improving vitamin D storage in fatty tissues and by creating a larger skeleton as a result of increased weight bearing (2). It should be emphasised that signs and symptoms that may uncover secondary OP should be searched for so that underlying condition must be treated in order to insure success with specific treatment for OP.

BONE MARKERS
Substances released in the process of bone formation and resorption may be measured and indicate high or low bone turnover states. Most common formation markers include: osteocalcin, type I procollagen peptides (PINP and PIIINP) and bone specific alkaline phosphatase (BALP). Deoxypyridinoline and cross-linked N- and C-telopeptide of type I collagen (NTx and CTx) are markers of bone resorption (10). Of these markers the urinary NTx and the serum osteocalcin are the most available and specific. Currently there are no definitive guidelines on the use of bone markers because of the tremendous variability in the values in a single patient and among patients in a single group (10). However, they may be useful in some patients for monitoring early response to therapy as marker will show the effect of treatment much faster (3–6 months) than bone density measurements which usually require 1-2 years of an intervention to register a significant change (6,10). Also the level of bone turnover is important indicator in treatment decision making.

PREVENTION AND TREATMENT

1. NONPHARMACOLOGIC MEASURES
Dietary recommendations - Adequate calcium (Ca) and vitamin D are important for persons at any age, particularly in childhood, during the bone acquisitions process. Postmenopausal women should ingest 1200-1500 mg of elemental Ca daily; other groups, without OP risk factors, 1000 mg (11). Adequate vitamin D is required for optimal Ca absorption. Vitamin D also improves muscle function, probably through increase in muscle protein synthesis. The RDA of 400 IU of Vitamin D may not be adequate for the elderly, so supplementation to 800 IU is recommended for that age group.
Physical activity and lifestyle modification - Bone growth is stimulated by physical stress. Life-long weight-bearing exercise is the best insurance for building peak bone mass and preventing critical age-related decline. Activities in the upright posture such as walking, running and jumping are the most effective. High intakes of alcohol and caffeine are risk factors for OP, so consumption of both should be moderate. Smoking is another risk factor, so measures to quit smoking could be necessary.

2. PHARMACOTHERAPY
Estrogen - estrogen stimulates bone formation in endosteal sites and inhibits bone resorption. The Women’s Health Initiative (WHI) showed decreased hip and vertebral fractures in patients taking estrogen (12). Estrogen increases bone density during the time of treatment but as soon as estrogen is stopped bone density starts decreasing (13). Because the WHI did not show the protective effect against heart disease that had been assumed and because of the increased incidence of breast cancer, estrogen is no longer recommended for primary prevention of OP. It may be used with careful monitoring for OP treatment in patients who cannot be helped by other agents.
Calcitonin (Miacalcin Nasal Spray or Injection) - this 32-amino acid peptide derived from the parathyroid glands modulates serum calcium levels by inhibiting resorption, primarily at vertebral sites. This action
is mild compared with other antiresorptive agents. No study has demonstrated a significant decrease in fracture risk. Calcitonin has the interesting effect of decreasing the pain of recent vertebral fractures. Selective estrogen receptor modulators (SERMs) - estrogen-like compounds that have differing effects on estrogen receptors have been developed. Tamoxifen is antagonist on breast tissue and decreases recurrence and secondary primaries in postmenopausal breast cancer patients. Tamoxifen does have weak agonist effects on bone and causes an increase in bone density. Raloxifene (Evista) was specifically developed to treat OP and has a stronger agonist effect on bone, midway between estrogen and tamoxifen. Raloxifene decreases vertebral fracture incidence but not hip fractures. One proposed mechanism is that the antiresorptive effect of raloxifene is sufficient to stop osteoclasts from perforating the trabeculae, preserving the cancellous bone architecture, but that a stronger antiresorptive drug or bone-forming drug is required to increase cortical bone. Raloxifene is antagonist on the uterus, and also decreases the incidence of estrogen-positive breast cancer. Other SERMs are currently being developed, such as basedoxifene and lasofoxifene.

THE BISPHOSPHONATES:
ALENDRONATE, RISEDRONATE, INANDRONATE, ZOLEDRONATE
These oral agents bind to the active resorption sites in bone and inhibit the action of osteoclasts. Both alendronate (Fosamax) and risedronate (Actonel) have been shown to increase bone density and reduce fracture rate at both vertebral and nonvertebral sites compared with placebo. Both can be taken for prevention or treatment of OP. Although initial studies were on daily dosage, further research has now shown that both drugs can be taken weekly. This way of administration reduces serious GI irritation, especially in the esophagus. The dosages of alendronate are 5 mg/day or 35 mg/week for prevention and 10 mg/day or 70 mg/week for treatment of OP. For risedronate the doses are 5 mg/day and 35 mg/week for both indications. The third agent is ibandronate (Boniva), approved in 2005 for a daily dose of 2.5 mcg or a monthly dose of 150 mcg. It has the same GI side effects as the other bisphosphonates but monthly exposure is thought to decrease the risk and frequency of side effects. Zoledronate (Zometa) an intravenous bisphosphonate used for hypercalcemia and malignancies, is now being tested as a once-a-year treatment in postmenopausal women. Parathyroid Hormone (PTH), Teriparatide (For-
biphosphonates, as blocking resorption drugs had showed no additive effect. BMD gain with a combination of PTH and alendronate was midway between gains by each drug separately, PTH causing the greatest gains. (20).

On the other hand, using the drugs sequentially is advantageous (21). Alendronate sustains bone density after the withdrawal of estrogen or PTH treatment (13,20).

**CONCLUSION**

Osteoporosis is a global major health problem. Although identified as the second world healthcare problem, currently it is widely underdiagnosed and undertreated condition as it is mostly asymptomatic until a fracture occurs. With recommended preventive guidelines, we should firstly emphasise prevention of the disease with dietary and lifestyle measures from the early childhood and secondly make more efforts to detect and treat potential cases in a timely manner to avoid serious complication of the disease with devastating effect to quality of life of affected individuals. In that way we should significantly reduce morbidity and mortality rates and reduce significant economic and social burden imposed by this costly disease.

**REFERENCES**


