General Overview about Osteoporosis and its effects on Health

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Conflict of interest: None declared
Funding: No funding sources

Abstract

Background: Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. This well-established definition, developed by international consensus, comprises both adverse effects of osteoporosis on bone mass and microstructure, and the clinical outcome of fracture. The prevalence of osteoporosis in Egypt was 28.4% in women and 21.9% in men. Furthermore, 53.9% women and 26% men had osteopenia. Hip and vertebral fractures are strongly associated with reductions in hip BMD and spine BMD, respectively, and have historically been considered the prototypical osteoporotic fractures. However, the incidence of all other fractures (non-hip, non-vertebral) is numerically much greater and collectively these fractures result in much larger economic costs for the population. The lifetime risk of any osteoporotic fracture is 40% to 50% for women and 13% to 22% for men, a markedly higher risk when compared with other major diseases.

Tob Regul Sci.™ 2023;9(1): 242-250
DOI: doi.org/10.18001/TRS.9.1.16

Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. This well-established definition, developed by international consensus, comprises both adverse effects of osteoporosis on bone mass and microstructure, and the clinical outcome of fracture. According to the World Health Organization (WHO) diagnostic criteria, using standard deviation scores of bone mineral density (BMD) related to peak bone mass in healthy young women, with osteoporosis being defined as a BMD T score of –2.5 or less **(1).**

The diagnostic criteria recognized the importance of low BMD in the pathogenesis of fragility fractures and provided a tool that could be used in epidemiological studies to quantify the prevalence of osteoporosis. However, the utility of BMD as a clinical indicator of osteoporosis is limited, because

BMD is only one of a number of important risk factors for fracture, and the majority of fragility fractures occur in individuals with BMD values above this threshold **(2).**

Epidemiology:

The prevalence of osteoporosis is rising steadily and becoming a major public health issue, largely due to associated morbidity and mortality, which is especially relevant with the universal increasing life expectancy; in particular, more rapidly in the developing countries. For example, it is projected that by 2050, Egypt will be close to 130 million inhabitants, and more than 30% of its population will be aged 50 years and over **(3).**

Women are eight times more at risk of osteoporosis than men, about 200 million women worldwide suffer from the disease. The prevalence of osteoporosis in Egypt was 28.4% in women and 21.9% in men. Furthermore, 53.9% women and 26% men had osteopenia. In addition, 74.9% of patients admitted with hip fractures had osteoporosis **(4).**

Approximately 10 million Americans over the age of 50 have osteoporosis, with a further 34 million at risk of the disease. By 2025, costs and annual fracture incidence are anticipated to rise by almost 50%, with a greater than 87% rise for those aged 65 to 74 years. Worldwide, osteoporosis causes more than 8.9 million fractures annually **(5).**

Hip and vertebral fractures are strongly associated with reductions in hip BMD and spine BMD, respectively, and have historically been considered the prototypical osteoporotic fractures. However, the incidence of all other fractures (non-hip, non-vertebral) is numerically much greater and collectively these fractures result in much larger economic costs for the population **(2).**The lifetime risk of any osteoporotic fracture is 40% to 50% for women and 13% to 22% for men, a markedly higher risk when compared with other major diseases. The burden from osteoporosis related fractures is long lasting. It is estimated in European Union that fragility fractures lead to annual loss of quality-adjusted life years totaled more than 2.6 million and it is the fourth leading cause of chronic disease morbidity **(6).**

- **Clinical presentation and complications:**

Osteoporosis is a hidden disease which symptoms typically do not appear until the occurrence of a broken bone and even minor stress may induce fractures when BMD is decreased. Osteoporosis develops gradually without warning signs or symptoms. It remains silent until fractures occur **(1).** The main clinical manifestations of osteoporosis are due to its complications, fractures. The fracture is both a sign and a symptom of osteoporosis **(7).**

A fragility fractures are very common in osteoporotic individuals that may be defined as a pathological fracture that results from minimal trauma (e.g. a fall from a standing height) or no identifiable trauma at all. **(8).**

Typical fractures in patients with osteoporosis include vertebral (spine), proximal femur (hip), distal forearm (wrist) and proximal humerus **(8).**

Fractures may cause chronic pain, disability and death. These fractures are responsible for lasting disability, impaired quality of life, and increased mortality, with enormous medical and heavy personnel burden on both the patient's and nation's economy **(7).**

Vertebral compression fractures are the most common sequelae of osteoporosis. The actual incidence of vertebral fractures is likely much greater given the large number of vertebral fractures that go undetected, with only a third of vertebral fractures clinically diagnosed. Vertebral fractures might occur during daily chores without any trauma or fall. Existence of vertebral compression fracture increases the risk of future vertebral compression fractures where with one fracture, there is a fivefold increase; with two or more fractures, there is a 12-fold increase **(9).**

Symptomatic patients may present with back pain and fracture demonstrated on radiography, most commonly between T8 and L4. Patients with an acute fracture may report abrupt onset of pain with position changes, coughing, sneezing, or lifting. Chronic vertebral compression fractures may present with loss of height in addition to kyphosis. Its complications include bone loss, muscle weakness, pressure sores, ileus, urinary retention, impaired respiratory function, venous thromboembolism, and spinal cord compression **(10).**

The first complaint of the patient with vertebral fracture might be the loss of height caused by vertebral compression due to fractures, which is more evident in the presence of multiple fractures; this abnormality can be objectively detected by increased occiput-to-wall distance caused by dorsal kyphosis (dowager's hump). Dorsal kyphosis is also seen in some older people without fractures so it is not a diagnostic criterion for osteoporosis **(7).**

Hip fractures are associated with 15–20% increased mortality rate within one year, followed by a 2.5-fold increased risk of future fractures **(7).** Approximately 20–50% hip fracture patients require long-term nursing homecare and suffer from decreased quality of life, social isolation, depression, and loss of self-esteem **(11).**

Osteoporosis has traditionally been considered a disorder of postmenopausal women, but low bone mass and accelerated bone loss can also occur early in life causing premenopausal osteoporosis. There are a few risk factors that increase a woman's risk of premenopausal osteoporosis, including inadequate nutrition, physical inactivity, hormonal, drugs and medical diseases. The study by **Mahboub et al. (12),** showed that 24.8% of the premenopausal females had osteopenia with a significant correlation between having osteoporosis and increasing age, fertility period, parity, and the presence of comorbidity, especially hypertension, and diabetes mellitus. Vitamin D deficiency is an important risk factor for osteoporotic fractures in all age groups especially among elderly population. Prevalence of vitamin D deficiency in elderly patients with hip fractures varies from 50 to 62% in different population in various geographical areas **(3).**

Heredity also plays a role in the development of osteoporosis. The most important examined gene linked to osteoporosis is VDR gene. There are numerous known polymorphisms in VDR, some of them are established to be associated with bone diseases as osteoporosis. For example, Fok1 A/G (rs2228570) polymorphism was significantly associated with osteoporosis in postmenopausal women **(13).**

- **Pathophysiology:**

Individuals continue to build bone and will reach peak bone mass at about 30 years of age, after which they begin to lose bone mass steadily **(1).** Throughout life, bones are remodeled, meaning that they are continuously resorbed by osteoclasts and replaced with new bone made by osteoblasts. This process allows for maintenance of mechanical strength and repair. An imbalance in remodeling activity in which resorption exceeds formation may result in the pathophysiological changes seen in osteoporosis **(5).**

Hormones and growth factors have a role in regulating bone function. Estrogen and testosterone have a significant effect on bone remodeling primarily by inhibiting bone breakdown. Cytokines that influence remodeling have also been identified, such as receptor activator of the nuclear factor kappa-B ligand (RANKL). RANKL is produced by osteoblasts that bind to RANK receptors on osteoclasts, leading to the activation and maturation of osteoclasts and culminating in bone resorption. Osteoprotogerin is also synthesized by osteoblasts and serves as a soluble decoy receptor blocking activation of RANK. **(14).**

Recently, cathepsin K is identified as a potent protease secreted by activated osteoclasts during the bone resorption process, resulting in the degradation of bone matrix and breakdown of mineral components of bone tissue **(1).** PTH plays an important role in bone formation by indirectly increasing the proliferation of osteoblasts through regulation of calcium homeostasis. Osteoporosis can be classified into two main groups by considering the factors affecting bone metabolism; primary osteoporosis and secondary osteoporosis **(7).**

- **<u>Primary osteoporosis:</u>**

Primary osteoporosis is often associated with age and sex hormone deficiency. Age-related osteoporosis results from the continuous deterioration of the trabeculae in bone. In addition, the reduction of estrogen production in postmenopausal women causes a significant increase in bone loss **(1).**

Primary osteoporosis can also be divided into two subgroups **(15).:**

- Involutional Osteoporosis Type I: It is also known as postmenopausal osteoporosis, caused by the deficiency of estrogen, mainly affecting the trabecular bone.
- Involutional Osteoporosis Type II: It is also called senile osteoporosis, and it is related to bone mass lost due to the aging of cortical and trabecular bones.

- **Secondary osteoporosis:**

Secondary osteoporosis can be defined as a reduction of bone mass in which an etiological factor can be identified; this is most commonly represented by diseases or drugs affecting bone mass and/or bone quality, causing increased risk of fracture. Drugs are the most common etiologic factors responsible of secondary osteoporosis **(16)**

- **Diagnosis:**

- **Dual energy x-ray absorptiometry (DEXA)**

Osteoporosis is diagnosed radiographically based on BMD determinations from dual energy x-ray absorptiometry (DEXA) assessment. BMD should be measured at the hip and its subregions and the lumbar spine (posterior–anterior view of the L1–L4 vertebrae) using DEXA. Measurement of BMD at the hip is preferred for diagnosing osteoporosis because it is a strong predictor of risk for non-vertebral fracture, including hip fracture **(17).**

The diagnosis of osteoporosis is never taken as primary osteoporosis without ruling out the secondary causes. A good history and physical examination of the patient always reveal certain clues about the presence of another disease, certain special laboratory evaluations might be needed to rule out other responsible diseases **(7).** The most commonly recommended laboratory tests include serum 25(OH)D, calcium, creatinine, and thyroid-stimulating hormone levels. Referral to a subspecialist is indicated in patients with complex diagnostic issues **(17).**

- **Bone turnover biomarkers:**

Bone turnover occurs throughout life to repair fatigue damage and microfractures in bone and to maintain mineral homeostasis. Bone turnover biomarkers are produced from the bone remodeling process and can be measured in urine or serum. They are classified as; markers of bone formation, and markers of bone resorption. **(15).**

Markers of bone formation are total alkaline phosphatase, bone-specific alkaline phosphatase, osteocalcin, procollagen type 1 N-terminal propeptide, and procollagen type 1 C-terminal propeptide. **(18)**

Markers of bone resorption are hydroxyproline, deoxypyridinoline, pyridinoline, tartrate-resistant acid phosphatase 5b, carboxy-terminal cross-linked telopeptide of type 1 collagen, and amino-terminal cross-linked telopeptide of type 1 collagen. **(18)**

Biochemical markers of bone turnover may (19);

- Predict risk of fracture independently of bone density in untreated patients.
- Predict rapidity of bone loss in untreated patients.

- Predict extent of fracture risk reduction when repeated after 3–6 months of treatment with FDA-approved therapies.
- Predict magnitude of BMD increases with FDA-approved therapies.
- Help determine adequacy of patient compliance and persistence with osteoporosis therapy.

According to the current guidelines on osteoporosis management, bone turnover markers cannot diagnose osteoporosis, but its changes may be useful in monitoring osteoporosis treatment to confirm the efficacy of treatment and treatment adherence **(20).**

- **Fracture risk assessment tool (FRAX):**

As the main clinical manifestations of osteoporosis are due to its complications, fractures, FRAX score was developed as a tool for assessing the risk of fractures in people with osteoporosis. There is a robust correlation between BMD and fracture risk, with approximately a two-folds increase in fracture risk for every one standard deviation decrease in BMD. However, many or most patients with a hip fracture have a T-score better than -2.5. Thus, the diagnosis of osteoporosis alone does not fully capture all risk factors contributable to a person's fracture risk. The presence of clinical risk factors that are independent of BMD, particularly advancing age and prior fracture, can identify patients at high risk for fracture. The combination of BMD and clinical risk factors predicts fracture risk better than BMD or clinical risk factors alone. The most commonly used score is the FRAX, which has been incorporated in 120 guidelines worldwide **(6).**

Fracture risk assessment tools (e.g. FRAX) in handheld apps and computers which combine bone density score and risk factors, have provided rapid assessments of future osteoporotic fractures and can be performed at the bedside **(14).**

- **<u>Pharmacologic intervention:</u>**

The **National Osteoporosis Foundation (21)** recommends treatment for:

- Postmenopausal women with a personal history of hip or vertebral fracture
- T-score of –2.5 or less
- Combination of low bone mass (T-score between –1 and –2.5) and a 10-year probability of hip fracture of at least 3% or any major fracture of at least 20% as calculated by the FRAX.

The two key elements in treating osteoporosis are increasing the bone mass by using anabolic therapies (calcium supplements, short-term treatment with calcimimetics and PTH) and decreasing bone resorption through antiresorptive therapies (bisphosphonates, selective estrogen receptors modulators, anti-RANKL antibody and cathepsin K inhibitors) **(5).**

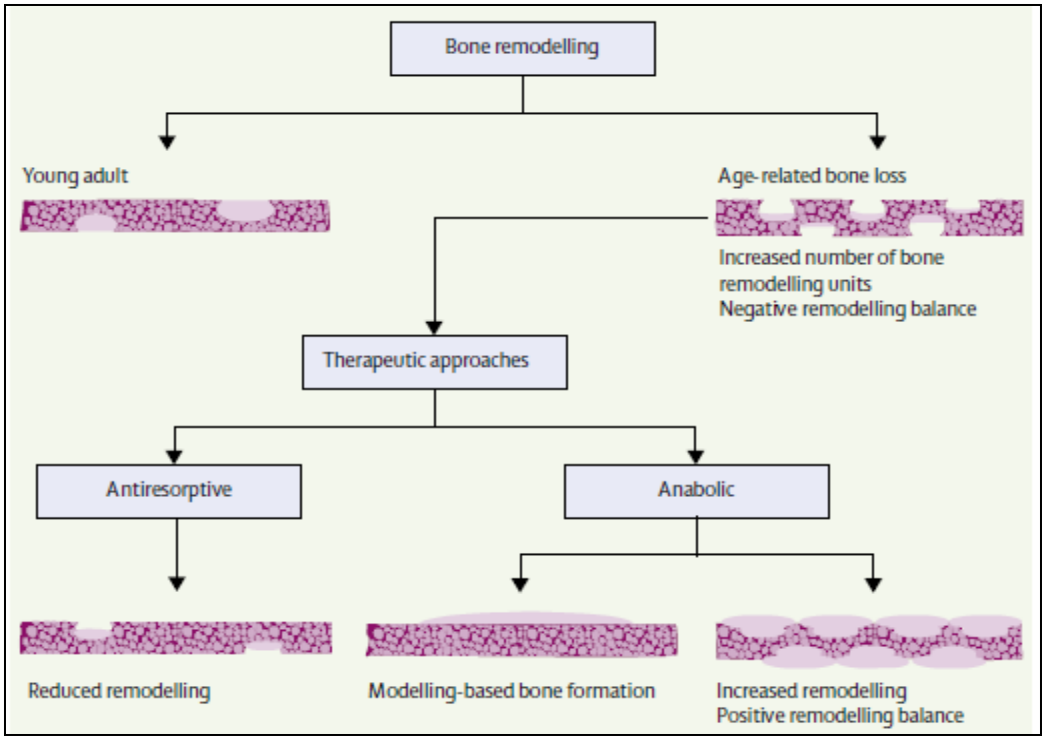

Figure (1): Effects of antiresorptive and anabolic drugs on bone remodelling and modelling **(2).**

Bisphosphonates are generally well tolerated and are considered first-line treatment. Bisphosphonates inhibit bone resorption through osteoclast function effects **(22).** Oral bisphosphonates should be taken with a glass of water on an empty stomach first thing in the morning to maximize absorption, and after administration, the patient should remain upright (sitting or standing) for at least 30 minutes to minimize the risk of reflux. These drugs are contraindicated in cases of esophageal stricture, achalasia, or Barrett esophagus; however, they are often tolerated in patients with a remote history of peptic ulcer disease or those with gastroesophageal reflux controlled with medications **(17).**

Raloxifene, teriparatide, and denosumab are alternative effective treatments for certain subsets of patients and for those who are unable to take or whose condition does not respond to bisphosphonates. Potential secondary causes must be considered for appropriate treatment **(22).** Specific therapy of these diseases, as well as antiresorptive and anabolic drugs, improve BMD, but without evidence of fracture reduction **(23).**

Because fracture risk increases rapidly after initiation of glucocorticoid therapy, bone protective treatment should be started as early as possible in high-risk individuals. Alendronate, risedronate, zoledronic acid, denosumab, and teriparatide are all approved for use in glucocorticoid treated patients at increased risk of fracture, because of their effects on BMD **(2).**

Duration of medical treatment

In most people at high risk of fracture with irreversible risk factors, life-long management is usually required. Pivotal clinical trials of bisphosphonates have mostly been limited to three years, and evidence for their efficacy with longer treatment duration is based on the results of extension studies. Evidence has shown that fracture reduction is maintained for up to five years of treatment, but few data are available for effects beyond this period **(2).**

After initiation of treatment, the need for follow-up bone density testing is uncertain. A decrease in BMD could suggest treatment nonadherence, inadequate calcium or vitamin D intake, an unidentified secondary cause of osteoporosis, or treatment failure **(24).**

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