International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 1991-1998 www.ijprajournal.com ISSN: 2456-4494

An Overview and Management of Osteoporosis.

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Submitted: 18-04-2024 Accepted: 28-04-2024

ABSTRACT:
Osteoporosis is a bone disorder with remarkable changes in bone biological material and subsequent bone structure that affects millions of people worldwide from various ethnic groups. Bone fragility is a worse outcome of the disease that requires long-term therapy and medical care, especially in the elderly. So far, many involved genes including environmental factors have been established as disease risk factors, of which genes should be considered as effective biomarkers for early diagnosis, especially in individuals from high-risk families. In this review, we address and discuss a number of important criteria associated with osteoporosis.

KEYWORS: atherosclerosis, hyperparathyroidism, HPT, bone and hip fractures, bone mineral density, BMD

I. INTRODUCTION

Osteoporosis is a disease characterized by low bone mass, damage to bone tissue and disruption of bone microarchitecture: it can lead to reduced bone strength and increased risk of fractures. Osteoporosis is the most common bone disease in humans and represents a major public health problem. It is more common in whites, women, and older people. Osteoporosis is a risk factor for fracture just as hypertension is for stroke.[1] Osteoporosis affects vast numbers of people of both sexes and all races, and its prevalence will increase as the population ages. It is a silent disease until fractures occur, causing serious secondary health problems and even death. [2] Bone tissue is continuously lost by resorption and renewed by formation; bone loss occurs when the rate of resorption is greater than the rate of formation. Bone mass is modeled (grows and takes its final shape) from birth to adulthood: bone mass reaches its peak (referred to as peak bone mass (PBM)) at puberty; subsequently, bone loss begins.

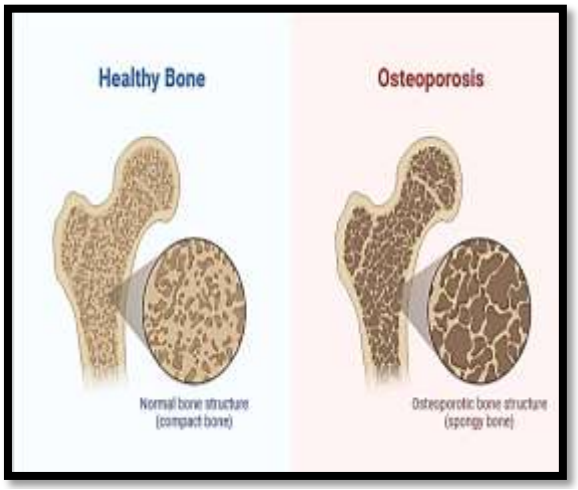

Fig 1: Osteoporotic bones

PBM is largely determined by genetic factors, health during growth, nutrition, endocrine status, gender, and physical activity. Bone remodeling, which involves removing older bone to replace it with new bone, is used to repair microfractures and prevent them from becoming macrofractures, helping to maintain a healthy skeleton. Menopause and advanced age cause an imbalance between the rate of resorption and formation (resorption is greater than absorption), increasing the risk of fractures. Certain factors that increase resorption more than formation also induce bone loss and reveal the microarchitecture. Individual trabecular bone plates are lost, leaving an architecturally weakened structure with significantly reduced mass; this leads to an increased risk of fracture, which is exacerbated by further age-related declines in function. A growing body of evidence suggests that rapid bone remodeling (as measured by biochemical markers of bone resorption or formation) increases bone fragility and fracture risk.

There are factors associated with an increased risk of osteoporosis-related fractures. These include general factors related to aging and sex steroid deficiency, as well as specific risk

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factors such as glucocorticoid use (which causes decreased bone formation and bone loss), decreased bone quality, and impaired microarchitectural integrity. Fractures occur when a weakened bone is overstressed, often from falls or certain daily tasks. [3]

II. CLASSIFICATION

Osteoporosis can be divided into two main groups according to factors affecting bone metabolism:

- **Primary osteoporosis**
- **Secondary osteoporosis**
- **Primary osteoporosis can also be divided into two subgroups:**

Involutional osteoporosis type I

It is also known as postmenopausal osteoporosis caused by estrogen deficiency, which mainly affects trabecular bone; therefore, women are more prone to osteoporosis than men, as evidenced by the male/female ratio of 4/5.7. [4]

Involutional osteoporosis type II

It is also called senile osteoporosis and is related to bone loss due to aging of cortical and trabecular bones. [5]

Secondary osteoporosis:

Osteoporosis can be caused by various diseases, medications and lifestyle changes

III. PATHOPHYSIOLOGY

Bones provide structure to the body, protection of organs, and a storehouse of minerals such as calcium and phosphorus, which are essential for bone development and stability. Individuals continue to build bone and peak bone mass at around age 30, after which they begin to gradually lose bone mass. Although peak bone mass is highly dependent on genetics, many modifiable factors such as diet, exercise, and certain diseases and/or medications can affect bone mass. [6]

Throughout life, bones are remodeled, meaning they are continuously resorbed by osteoclasts and replaced by new bone formed by osteoblasts. This process allows the maintenance of mechanical strength and repair. An imbalance in remodeling activity in which resorption exceeds formation may lead to the pathophysiological changes seen in osteoporosis.

Hormones and growth factors play a role in regulating bone function. Estrogen and testosterone have a significant effect on bone remodeling, mainly by inhibiting bone breakdown. Cytokines that influence remodeling have also been identified, such as receptor activator of nuclear factor kappa-B ligand (RANKL). RANKL is produced by osteoblasts, which binds to RANK receptors on osteoclasts, leading to osteoclast activation and maturation, culminating in bone resorption. [7]

Recent advances in bone molecular biology have identified a potent protease called cathepsin K (CatK). CatK is secreted by activated osteoclasts during the process of bone resorption, resulting in degradation of the bone matrix and breakdown of the mineral components of bone tissue.18 Parathyroid hormone (PTH) plays an important role in bone formation by indirectly increasing osteoblast proliferation through regulation. calcium homeostasis.

IV. ETIOLOGY

Primary Osteoporosis

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 post menopausal women causes a significant increase in bone loss.[9] In men, sex-hormone–binding globulin inactivates testosterone and estrogen as aging occurs, which may contribute to the decrease in BMD with time.[10]

Secondary Osteoporosis

Secondary osteoporosis is caused by several comorbid diseases and/or medications. Diseases implicated in osteoporosis often involve mechanisms related to the imbalance of calcium, vitamin D, and sex hormones [11] For example, Cushing's syndrome has been found to accelerate bone loss through excess glucocorticoid production. In addition, many inflammatory diseases, such as rheumatoid arthritis, may require the patient to be on long-term glucocorticoid therapy and have been associated with secondary osteoporosis. Notably, glucocorticoids are considered the most common medications linked to drug-induced osteoporosis. BMD has been found to decline rapidly within three to six months of initiation of glucocorticoid therapy. The American College of Rheumatology (ACR) has detailed recommendations to aid in guiding therapy selection for the prevention and treatment of glucocorticoid-induced osteoporosis (GIO). [12]

The causes of secondary osteoporosis may differ between the sexes. In men, excessive alcohol use, glucocorticoid use, and hypogonadism are more often associated with osteoporosis. For

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example, men who receive androgen-deprivation therapy (ADT) for prostate cancer are at increased risk of osteoporosis; Shahinian et al. found that 19.4% of those treated with ADT had a fracture compared to 12.6% of those who did not.[13]

V. RISK FACTORS FOR OSTEOPOROSIS

Osteoporosis is initiated by an imbalance between bone resorption and bone formation. Research studies point to a number of risk factors for osteoporosis that are modifiable, including diet and lifestyle factors, while some factors are uncontrollable [14]

Lifestyle changes	Genetic diseases	Endocrine disorders	Other
Vitamin D insufficiency	Cystic fibrosis	Central obesity	AIDS/HIV
High salt intake	Glycogen storage diseases	Cushing's syndrome	Amyloidosis
Smoking (active or passive)	Menkes steely hair syndrome	Diabetes mellitus (types 1 and 2)	Chronic obstructive lung disease
Alcohol abuse	Osteogenesis imperfecta	Hyperparathyroidism	Congestive heart failure
Immobilization	Riley–Day syndrome	Thyrotoxicosis	Chronic metabolic acidosis
Excessive thinness	Ehler Danlos	Hypogonadal states	Depression
Frequent falling	Hemochromatosis	Androgen insensitivity	End-stage renal disease
Low calcium intake	Marfan syndrome	Athletic amenorrhea	Hypercalciuria
Excess vitamin A	Gaucher's disease	Hyperprolactinemia	Idiopathic scoliosis

Table 1: risk factors involved in osteoporosis

I. Major non-modifiable risk factor

- Inadequate absorption of nutrients
- Lack of physical activity or risk of falling
- Weight loss
- Smoking cigarettes
- Alcohol consumption
- Air pollution
- Stress
- Main uncontrollable risk factors:
- History of falls
- Seniority
- Genus
- White ethnic background
- Previous fracture
- Reproductive factors (family history of osteoporosis)
- Secondary causes of osteoporosis
- Chronic use of certain drugs (long-term use of corticosteroids, etc.)
- Hypogonadism
- Hyperparathyroidism
- Chronic liver disease
- Inflammatory diseases (rheumatoid arthritis, etc.)
- Vitamin D deficiency
- Kidney disease (history of kidney stones)
- Cardiovascular disease
- Diabetes mellitus
- Dementia

II. Nutritional deficiency (especially eating junk food) and a sedentary lifestyle

Health promoting behaviors such as eating a healthy diet could reduce the impact of chronic diseases such as osteoporosis and cardiovascular disease.[15] Maternal diet has previously been found to affect bone mass in offspring, and good overall nutritional status with plenty of protein, calcium, vitamin D, fruit and vegetables has a positive effect on bone health, while a high-calorie diet and heavy alcohol consumption have been linked to lower bone mass and a higher fracture rate.[16] It is now established that a dietary pattern with a high intake of dairy products, fruit and whole grains can contribute positively to bone health, and strategies based on dietary patterns could have potential in promoting bone health.[17] A study of elderly Chinese women in Hong Kong confirmed this evidence, and similar investigations showed that higher scores on the "vegetables-fruits" and "snacks-beverages-dairy" patterns were associated with a reduced risk of cognitive impairment.[18]

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III. Alcohol consumption

Patients with osteoporosis should be regularly informed about smoking cessation, alcohol intake and estrogen status. Recently, a meta-analysis identified a non-linear association between alcohol consumption and hip fracture risk. Moderate alcohol consumption was inversely significantly associated with hip fracture risk, while heavy alcohol consumption was associated with increased hip fracture risk.[19] Alcohol consumption (low and moderate/high) can have a detrimental effect on bone health in both the cortical and trabecular compartments at the distal radius in men, and similar results were found in the trabecular and distal tibial compartments in women with minimal alcohol and low alcohol consumption. alcohol consumption, suggesting that avoiding alcohol may be beneficial for bone health [20]

IV. Smoking

Cigarette smoking is considered a risk factor for osteoporosis and is associated with bone loss and an increased risk of osteoporotic fractures.[21] Smokers had about a 10% decrease in circulating levels of 1,25-dihydroxyvitamin D (1,25(OH)2D). Smoking is associated with increased amounts of follicle-stimulating hormone and luteinizing hormone, which leads to a drop in estrogen levels and leads to rapid bone loss. The influence of some risk factors of osteoporosis and their role in the regulation of bone formation and bone diseases.[22]

V. Genetic factors

The genetics of osteoporosis represents one of the greatest challenges and the most active area of research in bone biology. It is well known that variation in BMD is determined by our genes. Some candidate gene polymorphisms in relation to osteoporosis have been implicated as determinants of BMD. Among the most intensively studied are the vitamin D receptor gene (VDR), the type I collagen α1 gene (COLIA1) and the estrogen receptor-α gene (ERα). VDR modulates the transcription of target genes involved in calcium uptake or bone formation, including calcium-binding proteins.[23]

VI. Medicines

Synthetic glucocorticoids are administered to treat disorders caused by autoimmune, pulmonary, and gastrointestinal diseases, as well as in organ transplant and malignancy patients.[24] Glucocorticoids cause profound effects on the skeleton, and glucocorticoid-induced osteoporosis is the most common secondary cause of osteoporosis.[25] Glucocorticoids induce a biphasic bone loss with a rapid initial phase showing 10–20% bone loss after only 3 months of treatment and a slower phase of 2–5% bone loss per year.[26]

VII. Hyperparathyroidism

Primary hyperparathyroidism (PHPT) is a disorder of calcium metabolism with the highest incidence in postmenopausal women. It acts on kidney cells by increasing renal tubular calcium reabsorption and also by converting 25-hydroxy vitamin D (25-(OH)D) to 1,25(OH)2D by activating 1α-hydroxylase.[27]]

Rheumatoid Arthritis (RA)

RA is the most common form of inflammatory disease in adults characterized by progressive and systemic inflammation. RA is associated with osteoporosis due to active systemic inflammation, immobilization, and glucocorticoid use.[28] Osteoporosis occurs in two forms in RA: 1) generalized bone loss with an axial distribution including the spine, pelvis, hips, ribs, and humerus, and 2) periarticular or localized bone loss near inflamed joints.[29]

VIII. Dementia

Osteoporosis and Alzheimer's disease (AD) are common chronic degenerative disorders prevalent in the elderly. The vast majority of AD cases occur sporadically due to genetic mutation, aging, and environmental factors as pathogenic mechanisms. Osteoporosis is a multifactorial, mostly polygenetic disease, and no single factor can fully explain its occurrence. Common risk factors for both diseases include weight loss, vitamin D deficiency, less exposure to sunlight, and less physical activity.[30]

VI. PHARMACOLOGICAL TREATMENT

Most studies have focused on the effects of anabolic therapies and antiresorptive therapies on generalized bone loss.

a) Anabolic therapy

This type of osteoporosis therapy involves the use of drug components, i.e. recombinant hormones such as rhPTH (1-34); hPTH (1-84) for strengthening, stimulating bone synthesis and treating disease. [31]calcium supplements to prevent bone resorption and increase BMD; short-term treatment with calcimimetics and PTH to

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increase trabecular bone mass and cortical bone mass.[32]

b) Antiresorptive therapy

This type of therapy is used in the treatment of osteoporosis for its effect on strengthening the bones. The therapy consists of five types of chemical components, i.e. bisphosphonate, a class of antiresorptive drugs that can affect osteoclast activity.[33] hormone replacement therapy for the treatment of osteoporosis and especially for the relief of menopausal symptoms tibolone, a synthetic steroid used in early postmenopausal women that leads to an increase in BMD due to the expansion of selective ER modulators estrogen replacement therapy such as raloxifene used to treat postmenopausal osteoporosis increases BMD and reduces the risk of vertebral fractures,[34] bazedoxifene inhibits estrogen-induced responses in mammary glands in animal models and is used in conjunction with estrogen to treat menopausal osteoporosis and anti-RANKL antibodies and cathepsin K inhibitors, inducing an increase in bone mineral density (BMD) in a phase II study in patients with postmenopausal osteoporosis. [35,36].

VII. NON-PHARMACOLOGICAL OPTIONS FOR THE TREATMENT OF OSTEOPOROSIS

In addition to preserving skeletal muscle, resistance exercise has also been shown to increase bone strength through repeated mechanical loading, thereby improving bone mineral density and reducing the development of osteoporosis [37]. For example, a systematic review of 43 randomised controlled trials and found the most effective type of exercise for increasing neck of femur bone mineral density was high force exercise, such as progressive resistance strength training of the lower limbs.[38] In addition, correcting biomechanical imbalance in the abdominal trunk as well as strengthening hip flexion and knee extension has been shown to reduce the risk of falls and alleviate musculoskeletal pain [39]. Furthermore, smoking cessation, avoiding alcohol excess, optimising dietary intake of calcium and consuming a balanced diet rich in fruit and vegetables, with a slant towards an increased protein intake are modifiable factors contributing to the prevention of osteoporosis[40]. In general, these principles can also apply to the management of sarcopenia and by reducing the risk of falls and subsequent fracture through improved bone mineral density, acute decompensation and progression of the frailty syndrome can be mitigated[41].

VIII. NOVEL THERAPIES

a) Romosozumab

Romosozumab is a monoclonal antibody that binds sclerostin leading to increased bone formation and a decrease in bone resorption. It is administered as a monthly subcutaneous injection, at a dose of 210 mg. The FRAME study was an international, randomized, double-blind, placebo-controlled trial that compared Romosozumab with placebo in postmenopausal women aged 55–90 with osteoporosis. Both groups also received denosumab 6 monthly. The Romosozumab treatment arm showed a 75% lower risk of new vertebral fractures, at 24 months; with no significant difference in adverse events[42].

b) Dual inhibition of Dickkopf-1 (Dkk1) and sclerotin

Dkk1 is one of the antagonists in the Wntsignalling pathway which is an important cascade involved in bone formation. It was found that inhibition of sclerotin can lead to an upregulation of Dkk1 expression. Based on this, a study demonstrated the use of an engineered bio-specific antibody against sclerostin and Dkk1 simultaneously resulted in a bigger effect on bone formation compared to monotherapies in both rodents and primates. Improvements in healing and repair capacity of fractured bones were also seen when dual inhibition was used[43].

IX. CONCLUSIONS

The incidence of osteoporosis increases with age and the prevalence is increasing in line with global population ageing. Osteoporosis and sarcopenia often coexist and are associated with substantial burden for older people in terms of morbidity and mortality. Both are often underdiagnosed and undertreated. Routine assessment of bone and muscle health should be part of a holistic multidisciplinary led, personalised comprehensive geriatric assessment both in primary and secondary care. Nutrition, physical activity, exercise, gait and balance interventions have been shown to be beneficial for bone and muscle health and in reducing the number of falls. These should be instituted alongside other lifestyle measures as part of the treatment strategy for an older person.

Older people at risk of fracture derive considerable benefits from treatment with bone

sparing agents; the choice should take into account frequency, route of administration, cost, potential for polypharmacy, ADR and long-term survival. In clinical practice bisphosphonates and denosumab; either first line or for older people intolerant to bisphosphonates, have a strong evidence base for efficacy in older people. For those intolerant or who are unable to have bone sparing agents, calcium and vitamin D should be offered to maintain bone health.

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