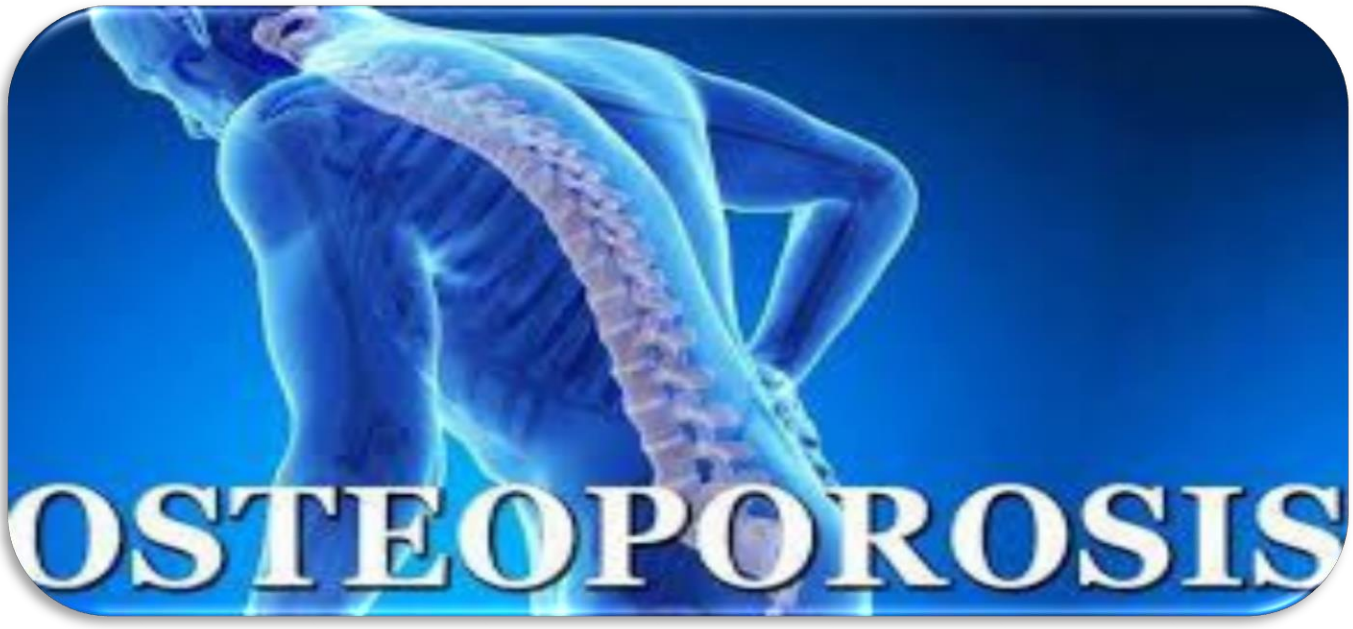
Minister of Higher
Education And
Scientific Research

University of Diyala
College of Medicine

Treatment of osteoporosis

submitted by
Muqdad Diyaa kadhim
Supervised by
Dr.moayed kadhim



INTRODUCTION

Osteoporosis is a more frequent disease in women than in men although mortality due to osteoporotic fractures is higher in men than in women .In addition, post-menopausal women suffer from osteoporosis and osteoporotic fractures at a higher frequency than pre-menopausal women. It is in- creasing in prevalence and remains largely underdiagnosed and undertreated. This is attributable in part to the fact that it is a clinically silent disease until it manifests in fracture. After this occurs, there can be significant pain, deformity, and increased morbidity and mortality.

The undertreatment of patients with osteoporosis is a serious issue. After patients are diagnosed with osteoporotic fractures, they may not receive appropriate medical treatment.

Types of osteoporosis:

Osteoporosis is mainly of two types. They are:

1- **Primary osteoporosis:It occurs in both genders at all ages but often follows menopause in women and occurs late in life in men.**

a- Primary Osteoporosis Type I (or) Postmenopausal Osteoporosis: It is characterized by an increased bone resorption that primarily affects trabecular bone and is directly linked to the decreased production of estrogen that coincides with menopause. Rapid bone loss is osteoclast-mediated and occurs in women within the first 5 to 10 years after menopause.

b- Primary osteoporosis Type II:Here, proportionate loss of trabecular and cortical bone occurs usually due to a decrease in bone cell activity accompanying aging. This type of osteoporosis predominately afflicts men and women over the age of 70 years and is called senile osteoporosis.

2- Secondary osteoporosis:This is a condition where osteoporosis occurs as a result of an identifiable cause. There are several causes for secondary osteoporosis which include:

(i). Endocrine disorders like: Acromegaly, adrenal atrophy in Addison disease, cushing syndrome.

(ii). Eating disorders like: Endometriosis, gonadal insufficiency (primary or secondary) hyperparathyroidism, hyper- prolactinemia, hyperthyroidism, hypogonadism, Type 1 diabetes mellitus.

(iii). Nutritional disorders like: Tumour secretion of parathyroid hormone–related peptide, gastro-intestinal disease.

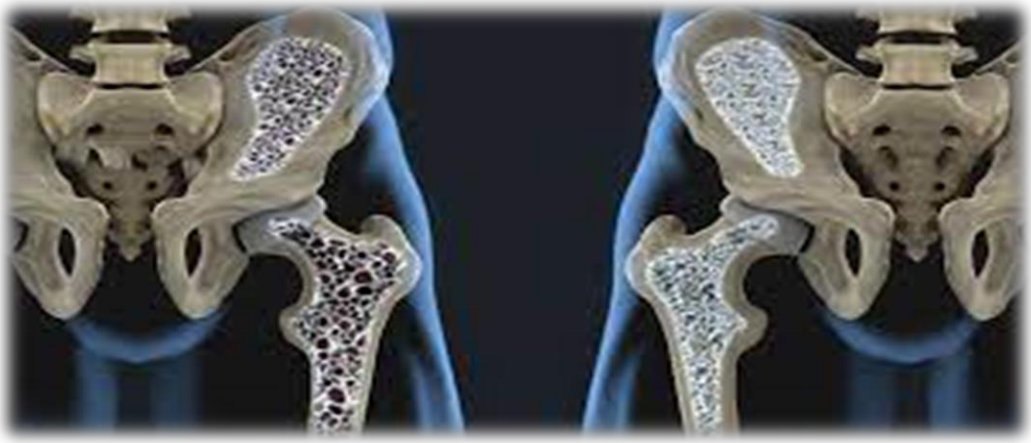
(iv). Alcohol-related liver diseases like: Celiac disease, chronic active hepatitis, chronic cholestatic diseases, gastrectomy, inflammatory bowel disease, jejunoileal bypass.

(v). Malabsorpion syndromes like: Pancreatic insufficiency, parenteral nutrition, primary biliary cirrhosis, severe liver disease.

(vi). Marrow-related disorders like: Amyloidosis, hemochromatosis, hemophilia, leukemia, lymphoma, mastocytosis, multiple myeloma, pernicious anemia, sarcoidosis, sickle cell anaemia, thalassemia.

(vii). Organ transplantation like: Bone marrow, heart, kidney, liver and lung.

(viii). Miscellaneous causes like: Ankylosing spondylitis, chronic obstructive pulmonary



Secondary causes of osteoporosis

Hypogonadal conditions, including:

- **Premature menopause**
- **Exercise oligomenorrhea**
- **Eating disorders Hyperparathyroidism Hyperthyroidism Type 1 diabetes**

Rheumatoid arthritis and other connective tissue diseases Malabsorption syndromes, including:

- **Celiac disease**
- **Bariatric surgery**
- **Pancreatic disorders Chronic liver disease Chronic kidney disease**

Chronic obstructive pulmonary disease Hematologic disorders, including:

- **Multiple myeloma**
- **Hemoglobinopathies**
- **Hematologic malignancies**

Risk factors:

Primary risk factors for osteoporosis	
Demographic Factors	**Behavioral Factors**
Advancing age	Current smoking
Female gender	Excess alcohol use (>2 standard drinks per day)
White or Asian race	Inadequate weight bearing exercise
Low body weight (<127 lbs)	Inadequate calcium intake
Taller height	Inadequate vitamin D intake
Family history	

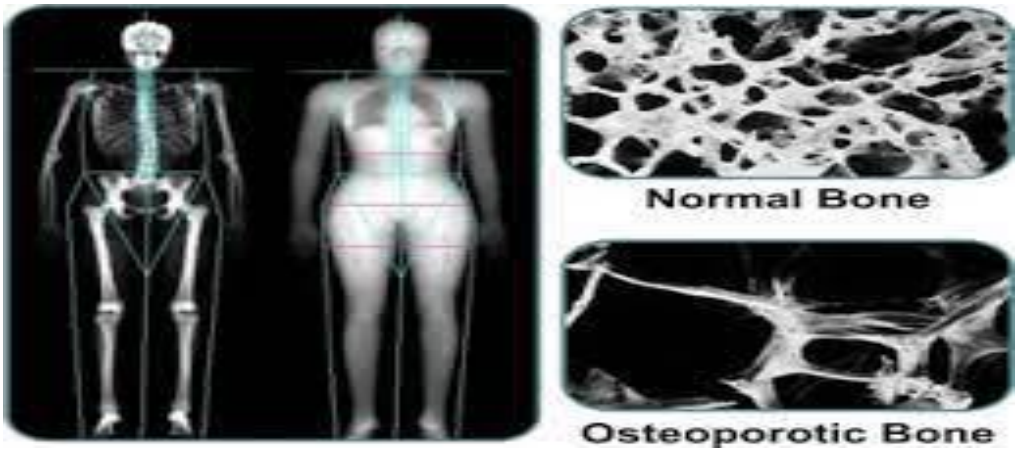
DIAGNOSTIC EVALUATION

Osteoporosis is diagnosed in the presence of any of the following conditions provided other bone conditions that mimic osteoporosis (eg, osteomalacia) have been excluded:

- **Screening DXA study T-score of —2.5 or less.**
- **Clinical fragility fracture regardless of bone density.**
- **Incidentally found (asymptomatic) vertebral compression fracture**

All patients should undergo a diagnostic workup to:

- **Evaluate the causes and contributory factors leading to low bone density;**
- **Exclude diseases that mimic osteoporosis;**
- **Assess the risk of subsequent fractures; and**
- **Select the most appropriate treatment.**



TREATMENT OF OSTEOPOROSIS

Although treatment is most frequently associated with a pharmacologic approach, it is important to recognize that for the optimal treatment of osteoporosis,nonpharmacologic approaches are also important to limit fracture risk. Nonpharmacologic interventions include limiting the risk of falls; using proper techniques when lifting; maintaining adequate intake of calcium, vitamin D, and protein; performing adequate weight-bearing physical activity and exercise to maintain or improve balance and posture; and making appropriate lifestyle changes, such as smoking cessation and moderating alcohol intake. These therapeutic adjuncts should be addressed with patients in addition to pharmacologic intervention.

Estrogen/Selective Estrogen ReceptorModulators:

Treatment of postmenopausal women with pharmacologic doses of estrogen was shown to have antiresorptive effects on the skeleton and to prevent bone loss. Bone histomorphometry has found that estrogen may also have local anabolic effects. In a longitudinal study in which iliac crest bone biopsies were performed to monitor response to therapy, pharmacologic estrogen treatment for 6 years resulted in increases of 61% in trabecular bone volume and 22% in

trabecular wall thickness. Despite this direct evidence of a beneficial role for estrogen in the treatment of postmenopausal osteoporosis and epidemiologic evidence from longitudinal imaging and fracture studies that found efficacy, the use of estrogen for the treatment and prevention of osteoporosis has waned considerably because of concerns related to the potential for nonskeletal adverse effects, as seen in the Women's Health Initiative study, and the availability of other agents with different safety profiles. Raloxifene is a selective estrogen receptor modulator (SERM) that is approved for treatment and prevention of postmenopausal osteoporosis. Most clinicians use raloxifene for the management of osteoporosis in patients with contraindications to other antiresorptive agents or for the treatment of women desirous of breast cancer prevention in whom enhanced skeletal health would be an additional benefit. Of note, the third-generation SERM bazedoxifene in combination with conjugated estrogens was recently approved by the US Food and Drug Administration (FDA) for the prevention of postmenopausal osteoporos

Bisphosphonates:

Unlike estrogen/SERMs that function as hormones/ hormone analogues by binding to cellular receptors to exert their functions, bisphosphonates are chemically stable inorganic pyrophosphate analogues with extremely high affinity for hydroxyapatite, the mineral component of bone.It is this property that allows bisphosphonates to achieve high local concentrations within the skeleton. Because of this extreme tropismfor bone, bisphosphonates exert important pharmacologic effects on skeletal disorders with enhanced or imbalanced bone remodeling, as frequently occurs with bone loss.Although no longer commonly used, first-generation non–nitrogen-containing bisphosphonates (clodronate, etidronate, and tiludronate) function bybecoming incorporated into nonhydrolyzable adenosine triphosphate (ATP) analogues. After osteoclastmediated endocytosis from the bone surface, these bisphosphonate-containing ATP analogues become cytotoxic, likely because of the inhibition of various ATP-dependent cellular processes, resulting in osteoclast apoptosis. All second- and third-generation bisphosphonates (alendronate, risedronate, ibandronate, and zoledronate) have nitrogen-containing side chains. Because of structural differences with first-generation

bisphosphonates, these second-generation bisphosphonatesadhere even more tightly to hydroxyapatite mineral in bone. In addition, after osteoclast endocytosis, they induce osteoclast apoptosis via a mechanism distinct from that of first-generation bisphosphonates, namely via inhibition of farnesyl pyrophosphate synthase (FPPS).As a result of FPPS inhibition, the posttranslational lipid modification of small guanosine triphosphate-binding proteins within osteoclasts is inhibited, again ultimately leading to osteoclast apoptosis. This inhibition of osteoclast function is most frequently monitored clinically via longitudinal assessment of changes in BMD, or more proximally via evidence of a reduction in serum or urine biochemical markers of bone resorption. Bisphosphonat skeletal uptake depends on delivery method. Oral bisphosphonates are minimally absorbed by the intestine, with o1% bioavailability due to their hydrophilicity, whereas intravenous preparations are 100% bioavailable. Bisphosphonates have variable potency for hydroxyapatite mineral binding and consequent variable binding-site availability, effect on bone turnover, and FPPS inhibition efficacy. Biologic half-lives of nitrogen-containing bisphosphonates remain a topic of debate, with data suggesting that those with the greatest potency for bone mineral may reside in the skeleton for Z5 years after administration.

Denosumab:

Denosumab is an antiresorptive agent that limits osteoclast-mediated bone resorption. Although bisphosphonates are small molecules, denosumab is a fully human monoclonal antibody that specifically binds RANKL, the master regulatory molecule required for osteoclast formation and activity, thereby preventing RANKL association with its cognate receptor RANK on the preosteoclast membrane and disrupting osteoclastogenesis. Denosumab is FDA approved for the treatment of osteoporosis and to prevent bone loss in men who receive androgendeprivation therapy for nonmetastatic prostate cancer and women who receive adjuvant aromatase inhibitor therapy for breast cancer who are at high fracture risk. As observed in the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial of 7868 women aged 60 to 90 years with a T-score between –2.5 and –4.0 at the lumbar spine or total hip, denosumab delivered subcutaneously every 6 months

for 3 years reduced new radiographic vertebral fractures by 68%, hip fractures by 40%, and nonvertebral fractures by 20% compared with placebo. In the subsequent FREEDOM extension study, treatment for an additional 3 years led to further increases in BMD at the lumbar spine, whereas the incidence of adverse events, including ONJ and AFF, remained low, albeit slightly higher than reported for long-term bisphosphonate treatment.In the long-term denosumab group (receiving 6 years of continuous denosumab) 4 oral events were adjudicated as consistent with ONJ during the first 3 years of the extension. Two of these patients discontinued denosumab treatment while the 2 others continued denosumab, with all 4 lesions healing with appropriate treatment. There was 1 midshaft and 1 subtrochanteric femoral fracture in the long-term group during the first 3 years of the extension, with neither of these determined to be an AFF after adjudication.

Teriparatide

Teriparatide (recombinant human parathyroid hormone, consisting of the amino-terminal 34amino acids of the amino acid native parathyroid hormone molecule) is the only FDA-approved skeletal anabolic agent. When injected subcutaneously once daily, teriparatide increases both bone formation and resorption, with formation outweighing resorption particularly in the initial 6 to 12 months of therapy, leading to increases in bone mass. The FDA has limited teriparatide treatment to 24 months lifetime. Because of the potential for osteosarcoma formation that depended on the dose and duration of treatment in a preclinical rat model, the FDA mandated a postmarketing analysis study that has not shown a causal relation between teriparatide treatment and osteosarcoma development in humans after 7 years of surveillance.79 As found in the Fracture Prevention Trial, in which postmenopausal women with a prior vertebral fracture were randomized to receive treatment with teriparatide or placebo for a median of 21 months, teriparatide treatment at the FDAapproved dose of 20 µg/d reduced new vertebral fractures by 65% and new nonvertebral fractures by 53%.80 Subsequent studies have examined treatment approaches in which teriparatide is given in combination with other agents, including estrogen,alendronate, zoledronate, and denosumab, with the most substantial increases in BMD found

to occur when denosumab or zoledronate was provided in combination with teriparatide. However, given the financial expense associated with teriparatide relative to other available pharmacologic agents, it is unclear how readily these provocative findings will translate to clinical practice.

New Agents for the Treatment of Osteoporosis

Finally, despite the availability of multiple medication classes for the treatment of osteoporosis, our evolving understanding of human bone biology has allowed for the continued development of new approaches to osteoporosis treatment. Of the agents currently in clinical trials, perhaps those with the greatest potential for changing clinical practice are inhibitors of cathepsin K and sclerostin. Cathepsin K, a cysteine protease expressed by osteoclasts, mediates bone resorption through its effects on collagen matrix degradation. In a Phase II clinical trial, the cathepsin K inhibitor odanacatib increased BMD at the hip and spine, and the study intriguingly found relative dissociation between measured biochemical markers of bone resorption and formation, with resorption markers decreasing to a greater extent than formation markers. Sclerostin, an osteocyte-secreted Wnt signaling antagonist, suppresses bone formation via its effects on osteoblast differentiation, activity, and survival. In a recent Phase II clinical trial of a humanized monoclonal antibody against sclerostin, substantial increases in bone mass at the spine and hips were observed.Perhaps most surprising was the observation that sclerostin antibody treatment appeared to simultaneously stimulate bone formation while suppressing bone resorption, which, if confirmed, would be a unique property among medications used for the treatment of osteoporosis. Phase III clinical trials for both agents are currently ongoing. Whether either agent will receive FDA approval is unknown, but if approved, both would be welcome additions to our current pharmacologic armamentarium for use in the treatment of osteoporosis.

CONCLUSIONS

Major advances have been made in understanding the pathophysiology of osteoporosis, with ongoing research devoted to more fully understanding the genetic and molecular causes of osteoporosis. It is increasingly clear that the

pathophysiology is complex and that causes of bone loss depend on the complex interplay of numerous genetic, hormonal, and molecular factors. The search for new targets for therapy continues, because all currently available agents were developed on the basis of the understanding of specific aspects of the pathophysiology. Eventual development of individualized therapy for osteoporosis will depend on recognition of the key genes and signaling pathways responsible for bone loss in a particular patient and application of therapies most likely to modulate the effects of these genes and pathways. Until individualized therapy is available, selection of osteoporosis treatment will continue to depend on assessment of patient-specific risk factors for bone loss and fracture, contraindications to therapy, patient preference, and cost.

Nonpharmacologic Treatment

Hip Protectors

Hip protectors, usually made of polypropylene, are a simple and efficacious device that can reduce the risk of hip fracture significantly. Some studies to date have shown that if used, these orthoses are successful in reducing hip fractures .Hip protector compliance rate has ranged in the literature from 35.9%28 to 48%.33 These orthoses may be difficult to manipulate, because most are in the form of undergarments that are difficult to wear and remove, particularly for elderly patients with poor balance and manual dexterity. In addition, patients with incontinence may have increased difficulties with the hip protectors. However, in addition to preventing hip fractures, hip protectors have been shown to improve self-confidence.

Posture Training Supports

Posture training supports have been shown to reduce symptoms associated with kyphosis and vertebral compression fractures. They are used in patients with symptomatic thoracic kyphosis, particularly secondary to vertebral compression fractures. The posture training support had better compliance than a conventional thoracolumbar support. Furthermore, there was an

increase in back extensor strength in patients compliant with the posture training support and postural exercise program. Back extensor strength, in turn, has been shown to reduce thoracic kyphosis and reduce vertebral fracture in estrogen-deficient women. However, there have been no prospective, randomized, controlled trials to date involving the posture training support.

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