ejpmr, 2018,5(8), 260-266

SJIF Impact Factor 4.897

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS

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Article Received on 04/06/2018 **Article Revised on 25/06/2018** **Article Accepted on 15/07/2018**

ABSTRACT

Osteoporosis occurs when bones lose their strength and density. Bones become fragile, weak and brittle and can cause fracture easily. Osteoporosis affects women after menopause and in their later years. The drop in estrogen after menopause is associated with increased loss of bone density for few years. Osteoporosis prevalent among older postmenopausal women increases the risk of fractures. Hip and spine fractures are associated with high morbidity and mortality among this population. Bone loss can be detected by measuring bone mineral density by densitometry. The primary goal of treatment of osteoporosis is to prevent a fracture which is accomplished by slowing /stopping bone loss, maintaining bone strength and minimizing that may contribute to fractures. This is achieved by change in lifestyle and diet and by pharmacological therapy.

INTRODUCTION

Osteoporosis, is a clinical condition visualized by reduced bone strength, is highly prevalent among postmenopausal women but also affects the men and women with a risk factor mediated by bone demineralization.[1] In the United States, about 10 million individuals are affected with osteoporosis with an age >50 years and 1.5 million are diagnosed with osteoporotic fractures each year.[2] As per WHO report, osteoporosis is globally recognized as a progressive systemic disease characterized by low bone mineral density and micro architectural deterioration in the brain that predisposes the patients to increased bone fragility.

After, the menopause, the osteoporosis is commonly prevalent in women.[1] Postmenopausal osteoporosis is clinical event where rate of bone loss exceeds the rate of bone formation. Generally, the menopause in women occurs during their midlife corresponding to the age between 40-50 years, which is an indicative of end of fertility potential of women. Thus the loss reproductive ability of women is due to decline in the production of female hormones, oestrogen and this process occurs period of years and is a natural consequence of aging The changes occurring during the transition can disrupt their daily routine activities. There are 1.5 million osteoporotic fractures every year, with an annual direct cost of treatment of $18 billion.[2] Fractures occur because of qualitative and quantitative deterioration in the vascular and cortical skeleton. In other words, the body is breaking down bone as it normally does but it is not producing new bone. As a result, bones become fragile and weak. It is harder to heal after a fracture when one has osteoporosis, presenting a double threat for people with this condition.[34,5] The menopausal transition is associated with bone loss that exceeds 4% per year and extends for 10 years or more Although, there is an individual variation to the rate and extent of bone loss.

Etiology: Women develop postmenopausal osteoporosis because estrogen rates declines after menopause. A lack of estrogen in postmenopausal women prevents the absorption and utilization of calcium and is the single most important factor in the development of osteoporosis in older women. As women grow older, they can lose significantly, their bone mass which results in osteoporosis. It may be identified during routine medical examination or in the wake of fractures which do not heal properly. Osteoporosis can affect almost the entire skeleton. The disease often does not become clinically apparent until a fracture occurs.[5]

The risk factors for osteoporosis are advancing age, low body weight, maternal history of osteoporosis, the direction of a fall and the most important, the presence of risk fractures-- fracture wrist, spine, proximal femur or humerus after mild /moderate trauma and those with osteopenia or spinal deformities.[6]

Table 1: Risk Factor Associated With Post-Menopausal Osteoporosis.

Risk Factor Associated With Post-Menopausal Osteoporosis	
Endogenous	Exogenous
Female	Low calcium intake
Asian/caucasian	Reduced physical
Small stature	Activity
Thin physique	Cigarette smoking
Family history	Alcohol abuse
Nulliparity	Aluminium antacids
Early menopause	Surgical menopause
Advanced age	Steroid therapy

Physiology of estrogen

Estrogens are naturally occurring steroidal hormones produced by the ovary, adrenal gland and during pregnancy by the placenta. The major estrogen produced by these organs is estradiol which are they synthesized from cholesterol. Estradiol is metabolized in the liver and form estriol and estrone, both of which are mildly estrogenic and are excreted in the urine. Estrogens are most implicated in the reproductive organs but also act upon other organ systems such as CVS, Skeletal, Immune, GIT, neural sites. Their major actions are genomic, mediated by nuclear organ receptors but they may also have non- genomic actions.[7]

Two types of estrogen receptors (ER_{α} and ER_{β}) have been detected in both males and females.[8,9] These receptors have different tissue distributions. ER_{α} is found in the tissue of the uterus, liver, breast, and kidney. ER_{β} is expressed in the reproductive tissues as well, but it is also seen in many nonreproductive tissues, including brain, bone, urinary tract, and the vascular system. The key components are the C or DNA binding domain, which binds with ligand binding affinity &sequence to DNA sequences in the promoter region of target organ, which binds estrogens &estrogen analogues.

Pathophysiology of osteoporosis

Bone remodeling is a biological event in old bone is replaced by new bone. This process consists of five phases as follows, the resting phase activation, resorption, reversal, and formation.

- During the activation phase osteoclasts are attracted to the bone surface.
- In the **resorption** phase, osteoclasts create an acidic status between the cell and bone surface, thus dissolving or resorbing the bone mineral content.
- During the reversal phase apoptosis of osteoclasts occurs and osteoblasts are attracted to the bone surface.
- In the **formation** phase, osteoblasts cause collagen deposition; and it gets mineralized to form a new bone.

Due to the estrogen deficiency during menopause and thus normal bone remodeling cycle gets affected. This leads to increase in osteoclastic resorption activity without a significant increase in osteoblastic activity and thus the amount of bone resorbed is higher than the amount deposited, which result in net bone loss. This process was originally described as 'uncoupling'. The cellular changes that occur in estrogen deficiency are now quite well understood. There is an increased production of Tumor necrosis factor (TNF-α) and cells of the stromal / osteoblastic lineage become more sensitive to IL-1. IL-1 and TNF stimulate stromal cells / preosteoblasts to release several cytokines- IL-6, macrophage colony stimulating factor (M-CSF), IL-11, granulocyte macrophage colony-stimulating factor (GM-CSF), transforming growth factor (TGF). The final cytokine in the osteoclastogenesis cascade is RANK ligand (receptor activator of nuclear factor B ligand) which is produced from osteoblasts and binds to its receptor RANK on osteoclasts.[10,11] RANKL has a natural antagonist osteoprotegerin (OPG) that is a soluble receptor that is secreted by the stromal osteoblast lineage cells. OPG is stimulated by estrogen.[12] In retrospect we now realize that the uncoupling factor secreted by the osteoblasts is RANKL. These factors increase bone resorption by increasing the pool size of pre-osteoclasts in bone marrow [10] (Pacifici et al., 1996) and are down

regulated by estrogen. The important action of estrogen is to increase OPG secretion,[12] and decrease M-CSF and RANK.[10,13]

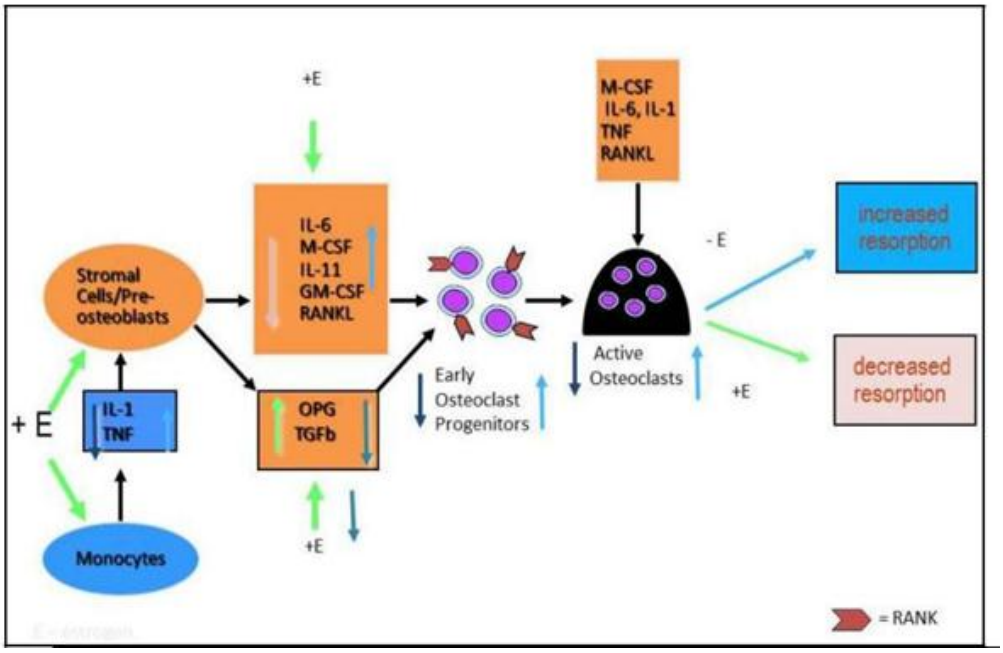

Fig. 1: Effect of estrogen on bone resorption.

Clinical manifestations

Postmenopausal bone loss progresses until the skeletal fragility leads to pain in the back, spine such as lumbar lardosis or kyphoscoliosis related to vertebral collapse. Overt fractures most often are of distal radius, femoral neck and vertebral bodies. Fractures in these three sites have a combined prevalence of 40 % in women > 65 years. These fractures result in 40, 00 -50, 00 deaths annually.[14]

Diagnostic evaluation

Bone quality cannot be measured clinically, but bone mineral density can be measured quickly and accurately. Bone mineral density should be measured in women with strong risk factors for osteoporosis. It should also be measured in those with osteoporosis related fractures. Several techniques are available for the measurement of bone mineral density. Among them the most useful is dual energy X ray absorptiometry. With this technique the density of the proximal femur is the most useful for predicting fractures. The measurement of lumbar or spine density is most useful for maintenance therapy. A T score of lower than -2.5 especially in the presence of risk factors, indicates the need for treatment to prevent fractures. T score of less than -1 or a Z score of less than -1 at the lumbar spine /proximal femur within five years after menopause at any age indicates the need to prevent bone loss. A z score of less than -2 indicates accelerated bone loss and needs further studies to identify the risk factor.[15] (Cohen and Shane, 2014).

Management strategies

It is important to screen the patients at risk and detect early bone loss in accordance with WHO standards. Postmenopusal women with established fractures should undergo an evaluation for osteoporosis that includes a comprehensive medical and family history and physical examination including vital signs and assessment of routine lab testing should be done. It should include C.B.C, serum calcium, phosphate, liver enzymes, total alkaline phosphates, creatinine & electrolyte levels, thyroid functioning testing and urinalysis [16] Treatment focuses on non-pharmacological measures such as balanced diet, adequate calcium and vitamin D intake, adequate exercise, smoking cessation, avoidance of excess alcohol intake and fall prevention. If pharmacological therapy is indicated, govt. approved options are calcitonin, biphosphonates, glucosamine, SERMS, Reclast, Teripatratide, transdermal estrogens and hormone replacement therapy,[15,17]

Calcium is most essential to bone health. The controlled clinical trials examining the effect of calcium on bone density and fractures in postmenopausal women, 15 trials (1806) patients were included that randomized post-menopausal women to calcium supplementation and recorded bone mineral density of the total body .The results showed that calcium supplementation alone has small effect on bone density but there as reduction in vertebral fractures [18]. Calcium supplementation mostly increases mineral density of non-weight bearing, cortical bone. Calcium salts are available in form of calcium carbonate, calcium citrate, calcium maleate, calcium gluconate, calcium hydroxide, calcium lactate, calcium sulfate, calcium pyrophosphate, calcium oxalate, calcium pantothenate salts. Calcium carbonate is absorbed more efficiently when taken with meals because it needs acid produced by the body when food is in the intestine. In contrast calcium citrate can be taken with or without food. Vitamin D increases body's efficiency at absorbing calcium. The best source of this vitamin is from sunlight. Many dietary modifications can help body absorb calcium more easily. A sodium and protein intake impairs calcium absorption, while added potassium helps

with the absorption. Caffeine and alcohol can decrease the body's ability to absorb calcium. The national institute of health adds that a diet high in fruit and vegetables shifts the acid base balance in the body, decreasing calcium absorption. The recommended dose of 1500 mg of calcium and 400-800 IU of vitamin D daily can stop bone loss for some postmenopausal women.[19]

Vitamin D: Calcitriol enhances absorption of calcium and phosphate from intestine.A recent 3 year follow up study substantiates that vitamin D and calcium supplementation in postmenopausal women with osteoporosis significantly alters bone mineral and organic matrix quality.[20] Factors that can affect vitamin D intake include decreased exposure to sunlight, decreased dietary intake and absorption problems. The body's use of vitamin D is enhanced in the presence of Mg and boron. Alfacalcidiol is orally active used in the dose of 1-2 microgms /day. It can increase bone mineral density and reduce fracture incidence in the elderly population. Cholecalciferol (vitamin D3) is used as granules for oral ingestion and oily solution for I.M injection. Calcitriol 0.25 -1 microgms is given orally daily or on alternate days.[21]

Magnesium: The other vital nutrients synergistically promote the maintenance of healthy bone tissue. For instances mega doses of calcium in absence of other minerals such as magnesium may contribute to abnormal soft tissue calcification Oral supplements with as much magnesium as calcium helps to prevent bone loss Mg increases the remineralisation of weight bearing trabecular bone in post-menopausal osteoporotic women. The daily dose of magnesium is 200-300 mg.[22] (Castiglioni et al., 2013).

Zinc: This vital trace element is essential for normal bone formation. It is involved in the biochemical activities of vitamin D. The daily requirement is 2-4 mg.[23]

Boron: Small amounts of this trace element can enhance absorption of calcium. The daily requirement is 2mg.[24]

Manganese: This trace element is essential for the mineralization of the bone as well as the production of cartilage and connective tissues. The best source of Mn in the diet is from grains [25].

Calcitonin: It is produced by C cells of the thyroid. It inhibits bone resorption by direct action on osteoclasts. Calcitonin is shown to reduce the risk of vertebral fractures but the effect on hip fracture appears to be less than that of biphosphonate therapy .It is used in post-menopausal osteoporosis as 100U s.c or I.M daily along with calcium and vitamin D supplements. However, given the limited efficacy of calcitonin in fracture prevention relative to other available agents and concerns about an increased risk of cancer with long-term calcitonin use, it is now rarely used for osteoporosis prevention or treatment [26].

Biphosphonates: Etridronate, Alendronate, risedronate are the currently approved biphosphonates used for the treatment of postmenopausal osteoporosis, which inhibit bone resorption. Alendronate is administered empty stomach in the morning with a full glass of water and patient is instructed not to lie down or take food for at least 30 min. It is available as 35 and 70 mg tablets. Recent data support the use of alendronate 10 mg daily in the treatment of steroid induced osteoporosis The dose of 5 mg daily has been shown to prevent accelerated bone loss in newly postmenopausal women &may be useful for women who are unable to take estrogen sensitive cancers or clotting disorders.

Calcium, iron, antacids, mineral water, tea, coffee, fruit juice interfere with Alendronate absorption. Side effects are gastric 1rritation, gastric erosion, flatulence, body ache. Etidronate is administered as orally or as intravenous. Adverse effects are gastric irritation, bone pain. The dose is 5- 7.5 mg /kg /day.[27]

Zoledronic acid, a bisphosphonate with greater antiresorptive potency, was approved for the treatment of osteoporosis in 2007. An annual infusion of zoledronic acid for 3 consecutive years (HORIZON PFT, n = 7765 women, age 65–89 years, neck T-score ≤ -2.5 or neck T-score ≤ -1.5 plus 1 vertebral fracture, 3-year follow-up) was effective in reducing by 70%, 41% and 25% the risk of vertebral, femur and non-vertebral fractures, respectively [28]. Zoledronic acid, owing to its great efficacy in reducing vertebral, non-vertebral and femoral fractures, as well as for its ease of administration and guaranteed absorption, can be the drug of choice in all scenarios where bisphosphonates are indicated.[29]

Strontium ralenate: It is also used for the treatment of osteoporosis in postmenopausal women. It is usually reserved for women who cannot take biphosphonates. In the dose of 2 gms, it has dual action of increasing bone formation as well as decreasing bone breakdown and it has been shown to decrease the risk of hip and spine fractures. Strontium seems to be associated with an increased risk of blood clots in the veins.[30]

Glucosamine: The most advanced dietary supplements for the management of bone and joint health include chondro- protective agents such as high quality glucosamine that may decrease the inflammation. A double blind clinical study states that glucosamine supplements may increase the cartilage and fluid that surrounds the joints or helps prevent breakdown of these substances .Glucosamine is a nutrient supplement that serves the purpose of cartilage building or lubrication of joints. Glucosamine helps the efficient working of joints and tissues. Glucosamine sulfate also plays a crucial role in the repair, maintenance and replacement of worn out or damaged tissues. It is an important constituent of body

cartilage, soft tissue that protects the joint. Glucosamine sulfate greatly helps in relieving the osteoporosis pain in knee joints .It is suitable and effective treatment for mild levels of arthritis as well as osteoporosis. The recommended dose of glucosamine sulfate is 100 mg in 1-2 capsules during the day at meal times with food. Side effects of glucosamine are very few.[31]

SERMS: Selective estrogen receptor modulators like raloxifene and tamoxifen have been marketed. Tamoxifen causes improvement in bone mass due to antiresorptive effect. Tamoxifen is effective orally. The dose is 10-20 mg BD. Raloxifene is an estrogen partial agonist in bone and CVS system. Raloxifene prevents bone loss in post-menopausal women. Raloxifene is absorbed orally but has low bioavailability due to extensive first pass metabolism. Its side effects are deep vein thrombosis and pulmonary embolism. The dose is 60 mg /day. It is preferably used in women who are 5 years past their menopause.[32,23]

Transdermal estradiol patches: In a clinical trial using transdermal delivery- 0.1 mg of 17 –beta -estradiol for days 1-21 and oral dose on day 11-21 of a 28 days cycle. Transdermal estradiol treatment is effective in postmenopausal women with established osteoporosis in only who had hysterectomy as the side effects of estrogen affect the other women with uterus.[33,24]

Teriparatide: is used for the treatment of osteoporosis in post-menopausal women with an increased risk of fractures. It works by decreasing the formation of bone and is given by daily injection under the skin in the abdomen or thigh. The recommended dose of teriparatide is 20 ug injected OD. It is good to take teriparatide at the same time each day. It decreases incidence of spinal fractures.[34,25]

HRT: Hormone replacement therapy remains a valuable option for the prevention of osteoporosis in elderly post - menopausal women. The choice of treatment depends on age, the presence /absence of prevalent fractures, esp. at the spine and the degree of bone mass density measured at spine and hip. The study of osteoporotic fractures provided epidemiological data that bone loss continues in older women &that estrogen may decrease this loss.Hormone replacement therapy is available as conjugated equine estrogens in the dose of 0.625 mg /day regularly or in cyclic fashion .plus medroxyprogesterone acetate 2.5 mg /day or estrogen therapy. In a study that was aimed to assess the antiresorptive effect of hormone therapy and oral ibandronate in postmenopausal osteoporotic women, authors measured BMD and bone turnover markers (C-terminal telopeptide of type I collagen) during the 6-month treatment period. There was an increase in BMD in both groups; however, the group on ibandronate had a significantly greater increase in BMD and reduction in C-terminal telopeptide than the group on HRT [35]. However, based on evidence of effectiveness, cost and safety, standard HRT should be considered one of the first-line therapies for the prevention and treatment of fractures in postmenopausal women, younger than 60 years,[36,37] But potential risks associated with HRT included are an increased risk of venous thrombosis, an exacerbation of preexisting liver disease for women with intact uterus taking estrogen alone and an increased risk of endometrial carcinoma. Serious side effects of hormone replacement therapy include enlarged and tender breasts, nausea, skin discoloration, water retention, weight gain, headache and digestive problems.

Denosumab (Prolia; Pralia) is a human monoclonal antibody which targets RANKL (receptor activator of NFjB ligand), a protein crucial for the differentiation of osteoclasts involved in bone resorption, which is clinically approved in USA and Europe.[38,39]

Denosumab binds to RANKL selectively and with high affinity preventing it from interacting and activating RANK (its receptor) on the surface of osteoclasts and their precursors. Consequently, the formation function and survival of osteoclasts is inhibited resulting in reduced bone resorption.[40-42]

Denosumab was effective in reducing fracture risk in women with PM osteoporosis in the randomized, doubleblind, FREEDOM study. Over 3 years, denosumab significantly reduced the risk of new vertebral fracture by 68% (primary endpoint), nonvertebral fracture by 20% and hip fracture by 40% relative to placebo.[43]

BMD, measured by DXA, was significantly improved with denosumab relative to placebo at various skeletal sites, including the total hip, lumbar spine, femoral neck and trochanter, over 3 years in FREEDOM.[44]

The recommended dosage of denosumab is 60 mg administered q6m via a single subcutaneous injection into the abdomen, upper arm or thigh.

Life style changes: Exercise greatly reduces the risk of heart disease, high B.P and diabetes. It has positive effects on mental well-being also. The sort of exercise that is beneficial in preventing osteoporosis is weight bearing such as walking or aerobics. Stopping smoking should be a priority to enjoy a longer life. Alcohol consumption should also be kept in safe limits.[45]

CONCLUSION

Osteoporosis represents an increasingly serious problem around the world. The economic burden of disease imposes is already considerable and will further grow as the population ages. It incorporates multiple modalities of therapy. In addition to early detection, patient education, exercise and nutritional supplementation, multiple therapeutic agents should be implemented early in an attempt to prevent initial and subsequent fractures.

Alendronate, raloxifene, risedronate, 1-34 fragment of parathyroid hormone and nasal calcitonin greatly reduced the risk of vertebral fractures. Calcium along with vitamin D is most important for increasing bone strength and vitamin supplementation is not sufficient to treat individuals with osteoporosis but is useful specifically in elderly women in care homes. Hormone replacement therapy remains a valuable option for the prevention of osteoporosis in post-menopausal women. Choice of treatment depends on age, the presence or absence of prevalent fractures, esp. at the spine and the degree of bone mineral density measured at spine and hip. Non- pharmacological intervention includes adequate calcium intake and diet, selected exercise programmes, reduction of other risk factors for osteoporotic fractures. The overall benefit versus risk assessment is a central focus in each of the clinical trial outcomes.

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