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"A Comprehensive Review On Hormone Replacement Therapy In The Prevention And Treatment Of Osteoporosis In Post Menopausal Women"

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Abstract: Osteoporosis is a systemic skeletal disorder characterized by decreased bone mineral density (BMD), leading to bone fragility and an increased risk of fractures. It is particularly prevalent in postmenopausal women due to estrogen deficiency, with significant variations in prevalence across regions. Osteoporosis can be classified into primary (age-related or postmenopausal) and secondary forms, the latter arising from various underlying conditions or medications. Postmenopausal osteoporosis, resulting from hormonal changes after menopause, significantly accelerates bone loss, particularly in the trabecular bone. The pathophysiology involves an imbalance between bone resorption and formation, exacerbated by estrogen deficiency. Risk factors for osteoporosis include non-modifiable factors such as age, gender, and family history, and modifiable factors such as smoking, calcium deficiency, and sedentary lifestyle. Diagnosis relies on bone mineral density (BMD) assessments through DXA scans, with treatment options including pharmacological therapies (e.g., hormone replacement therapy, bisphosphonates, and anabolic agents) and non-pharmacological strategies (e.g., dietary recommendations, exercise, and lifestyle changes). Effective management of osteoporosis involves a combination of medications, supplements, and lifestyle modifications to prevent fractures and improve quality of life.

Keywords: Osteoporosis, Bone Mineral Density (BMD), Postmenopausal Osteoporosis, Estrogen Deficiency, Hormone Replacement Therapy, Bisphosphonates, Anabolic Agents.

INTRODUCTION

Osteoporosis is a systemic skeletal disease characterized by porous bones with reduced bone mineral density (BMD) and it involves a decline in bone strength due to the loss of bone mass and the deterioration of the bone microarchitecture [1&2]. This results in increased bone fragility and a higher risk of fractures [2]. Overall, osteoporosis is three times more common in women than in men, because women have a lower peak bone mass, which is compounded by the hormonal changes that occur at the time of menopause [3].

EPIDEMIOLOGY OF OSTEOPOROSIS:

Osteoporosis is a major global health concern, particularly affecting postmenopausal women[3]. According to the WHO over 200 million people worldwide suffer from this disease by 2020 and will reach 12 billion by 2025, with varying prevalence rates across regions:

- **United States and Europe**: Approximately 30% of all postmenopausal women are affected by osteoporosis.
- **India**: Studies show a wide variation in the prevalence of osteoporosis in postmenopausal women, ranging from 25% to 62% [3&4].
- The incidence of osteoporosis-related fractures was reported as 725 per 100,000 person-years for men and 2,408 per 100,000 person-years for women, in both genders the rate of these fractures increased with advancing age [5]. This condition weakens bones, increasing the risk of fractures, which can lead to severe health outcomes [3]. **Notably**: Vertebral fractures: Those who have had a vertebral fracture are at significantly higher risk for future fractures, including a 2.3-fold increased risk of hip fractures (HF) and a 1.4-fold increased risk of distal forearm fractures and hip fractures, which are common in individuals with osteoporosis, are particularly dangerous, approximately 20% of women aged over 60 years die within one year after sustaining a hip fracture, illustrating the severe impact of osteoporosis on both morbidity and mortality [3].

CLASSIFICATION:

Osteoporosis can be classified into two main groups by considering the factors affecting bone metabolism [6]:

1. Primary osteoporosis.

2. Secondary osteoporosis

1. Primary Osteoporosis: It occurs as a part of the ageing process and according to a decrease in hormone levels in the body. As age progresses, the microstructure of the bones degrades, and BMD decreases, leading to an increased risk of fractures [2].

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

- **Involutional Osteoporosis Type I:** It is also known as postmenopausal osteoporosis, caused by the deficiency of estrogen, mainly affecting the trabecular bone; therefore, women are more susceptible to osteoporosis than men, as evident by a men/women ratio of 4/5.7.
- **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 [6].

2. Secondary Osteoporosis: It occurs due to secondary causes, including various medications used in the treatment of diseases including hyperparathyroidism, hyperthyroidism, anorexia nervosa, malabsorption syndrome, chronic renal failure, and Cushing syndrome leads to long term immobilization, long-standing secondary amenorrhea due to non oestrogen hormonal therapy, low body weight and excessive exercise leading to decreased bone mass and can also result in secondary osteoporosis, men are reported to have secondary osteoporosis more often than women [2&6].

Post-menopausal osteoporosis: It is also known as postmenopausal osteoporosis [6]. Menopause is defined as the cessation of menstrual bleeding following the stopping of ovarian follicle activity for nearly continuous 12 months at around the age of 50 years and menopausal transition occurs over several years and is considered a dynamic period during which women experience predictable changes in their menstrual cycle and decrease in bone density increases significantly, so that in the first 5–10 years after starting menopause, women lose approximately 25%–30% of their trabecular bone and 10%–15% of their cortical bone reserves and it is strongly believed that postmenopausal women are severely at increased risk of osteoporosis and

its complications [7]. It is caused by the deficiency of estrogen, mainly affecting the trabecular bone; therefore, women are more susceptible to osteoporosis than men, as evident by a men/women ratio of 4/5.7 [6].

PATHOPHYSIOLOGY:

- Oestrogen deficiency plays a critical role in the development of osteoporosis, particularly in postmenopausal women who are at the highest risk of the disease. Bone metabolism in postmenopausal women is characterized by high bone turnover, defined as the simultaneous increase in both bone resorption and bone formation. However, after menopause, bone resorption exceeds bone formation, resulting in an imbalance in bone remodeling and rapid net bone loss [8].
- Bone remodeling is the process by which old bone is replaced by new bone and the normal bone remodeling process consists of four phases: the resting phase activation, resorption, reversal, and formation;
  - In the **activation phase** of remodeling, osteoclasts are recruited to the surface of the bone.
  - In the **resorption phase**, osteoclasts generate an acidic microenvironment between the cell and the surface of the bone, dissolving or resorbing the mineral content of the bone.
  - In the **reversal phase** osteoclasts undergo apoptosis and osteoblasts are recruited to the bone surface.
  - In the **formation phase**, osteoblasts then deposit collagen; this is mineralized to form new bone [9].

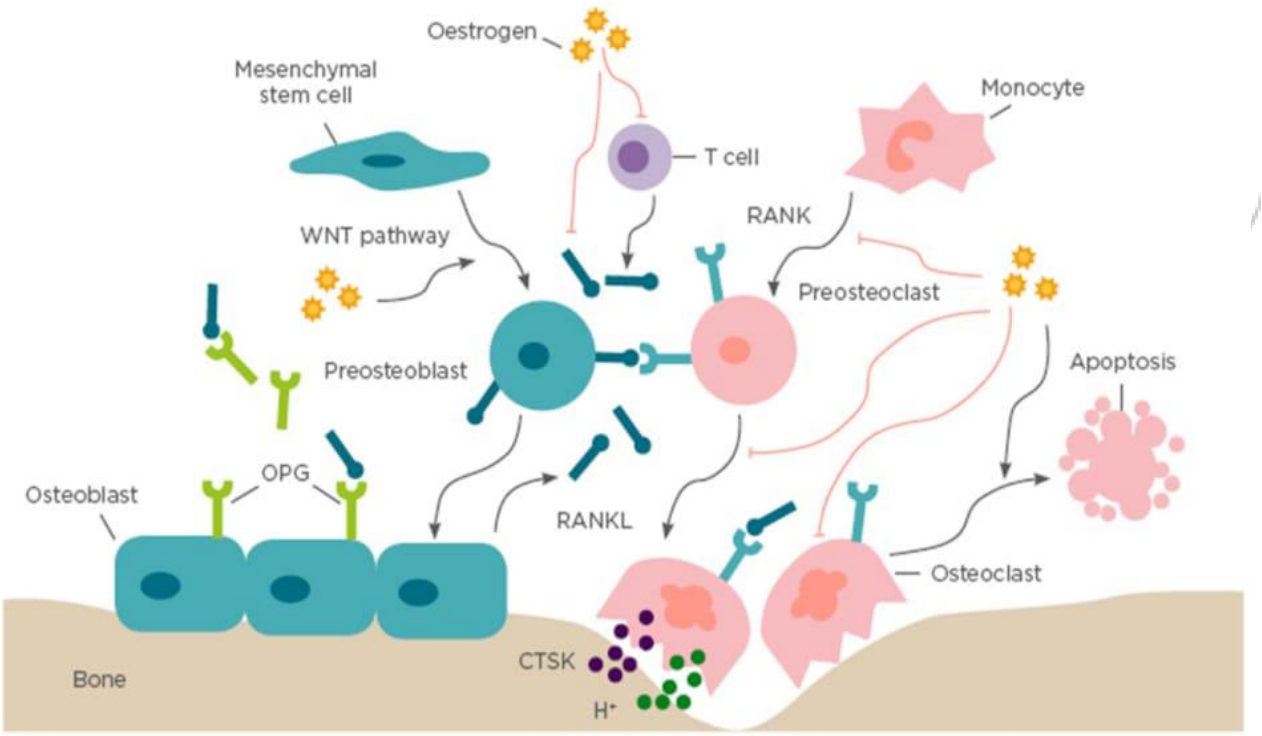

Figure:1 Bone remodeling involves a balance between osteoclast-mediated bone resorption and osteoblast-driven bone formation. Osteoblasts, derived from mesenchymal stem cells, create the extracellular bone matrix via the WNT signaling pathway. Osteoclasts, originating from the monocytic lineage, secrete resorptive factors through the RANK/RANKL/OPG signaling pathway. Estrogen regulates this process by inhibiting RANKL expression in T cells, mesenchymal stem cells, and osteoblasts, thereby reducing bone resorption. Key molecules include CTSK (cathepsin K), OPG (osteoprotegerin), RANK, and RANKL [8].

RISK FACTORS:

Osteoporosis is more common in females, mainly after menopause [2&10]

TABLE: 1 Risk factors of postmenopausal osteoporosis

MODIFIABLE	NON -MODIFIABLE
Smoking	Advanced Age
Inadequate calcium Intake	Female Gender
Vitamin D Deficiency	White/ Asian race
Low Body Weight	Low Peak Bone Mass
Estrogen Deficiency	Family History of Osteoporosis
Hypogonodism	Low BMI
Chronic Glucocorticoid Therapy	Personal History of Fracture

SIGNS AND SYMPTOMS:

Fragility fractures occur in the spine, wrist, and hip.

- They cause pain, limit activities, and reduce confidence.

- Early bone loss shows no symptoms.

Signs after bone damage:

- Back pain from a collapsed vertebra.

- Height loss over time.

- Stooped posture.

- Bones break easily [11].

DIAGNOSIS:

Diagnosis of osteoporosis is primarily based on bone mineral density (BMD) assessment via dual X-ray absorptiometry (DXA), expressed as a T-score, and the presence of fragility fractures. The WHO defines fragility fractures as those caused by minimal trauma, such as a fall from standing height or less, indicating reduced bone strength.

BMD categories:

1. Normal: T-score between +2.5 and –1.0.

2. Osteopenia: T-score between –1.0 and –2.5.

3. Osteoporosis: T-score below –2.5.

4. Severe osteoporosis: T-score below –2.5 with a fragility fracture [12].

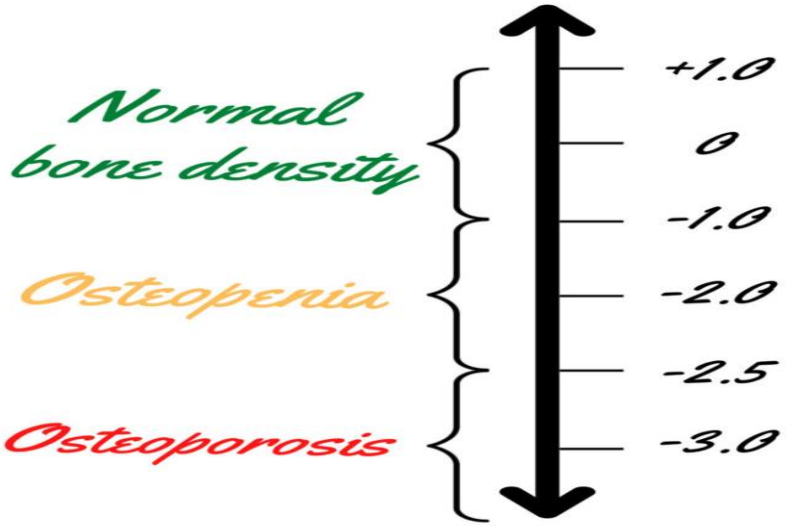

Figure: 2 T- score

Fracture risk can be estimated using models like FRAX, which calculates the 10-year probability of major fractures based on clinical risk factors. However, FRAX has limitations, as it does not account for all risk factors (e.g., physical activity, vitamin D deficiency, or detailed medication history) and excludes lumbar spine BMD. Since BMD alone is not cost-effective for population screening, it is best used alongside risk factors to identify high-risk individuals. Clinical assessment, including family/personal history and secondary causes of osteoporosis, is essential before initiating treatment [12&13].

TREATMENT:

Figure: 3 Management of post-menopausal osteoporosis

Pharmacological Treatments for Osteoporosis:

1. Hormone Replacement Therapy (HRT): Hormone replacement therapy can still be considered a first-line choice for the prevention of bone loss and fractures in the early postmenopausal period for up to 5 years in women with a low risk of adverse events classically associated with HT/ET and newer analyses show that treatment can be continued with an acceptable risk-benefit ratio, for many years the mainstay of preventing postmenopausal bone loss was hormone therapy, using estrogen + progestin (HT) or estrogen therapy (ET) for 6 months to rapidly reduce bone resorption and the use of estrogen in older women showed an increase of 6% in spine BMD, 5% in total hip BMD, and 4% in femoral neck BMD compared to placebo. Another study demonstrated increased spine BMD by 6.6%, femoral neck BMD by 3.2%, and total hip BMD by 3.1% compared to placebo, with greater effects observed when combined with alendronate. Two lower-dose studies also showed promising evidence of increased spine BMD [9].

TABLE: 2 Commonly used oestrogens and progestins

Route	Oestrogens	Dosage
Oral	Conjugated estrogens (conjugated equine oestrogens)	0.625 mg
	Micronized 17 beta oestradiol	1, 2 mg
	Oestradiol valerate	1, 2 mg
	Estropipate (piperazine estrone sulphate)	0.75, 1.5, 3 mg
Transdermal	17 beta oestradiol (patch)	25, 37.5, 50, 75, 100 µg/day
	Oestradiol (gel)	1 mg/ 1g
Subcutaneous	Oestradiol (implant)	20, 50, 100 mg
Vaginal	Estriol (gel)	1mg/g
	Estradiol (tabs)	25µg
	Progestins	
Oral	Norethisterone acetate	0.5, 1 mg
	Medroxyprogesterone acetate	2.5, 5 mg
	Chlormadinone acetate	2, 5, 10 mg
	Drospirenone	2 mg
	Dydrogesterone	5, 10 mg
	Nomogestrol acetate	3.75, 5 mg
	Promegestone	0.125, 0.25, 0.5 mg
	Micronized progesterone	100, 200 mg
Transdermal	Levonorgestrel	7, 10µg/24h
Intrauterine	Levonorgestrel intrauterine device	20 µg/24h

Benefits of HRT:

- **Symptom Relief:** HRT is among the most effective treatments for managing menopausal symptoms, such as hot flashes, night sweats, and vaginal dryness. It can greatly improve the quality of life for women dealing with these symptoms.
- **Bone Health:** Estrogen is crucial for maintaining bone density, and HRT helps prevent osteoporosis and fractures in postmenopausal women.
- **Cardiovascular Health:** Research indicates that HRT may offer cardiovascular benefits, particularly for younger postmenopausal women, by improving lipid profiles and reducing the risk of coronary heart disease [14].

2. Anti-Resorptive Agents: Prevent bone resorption and loss.

Bisphosphonates: Suppress bone turnover.

Examples:

- Alendronate-10mg/day or 70mg per week orally:
  Reduces spine fractures by 50%. Effects last after discontinuation.
- Risedronate-5mg/day or 35mg per week orally:
  Reduces spine fractures by 41%, non-spine fractures by 39%.

- Zoledronic Acid-5mg yearly IV:
  Reduces spine fractures by 70%, hip fractures by 41%.
- Ibandronate-2.5mg/day or 150mg per month orally:
  Effective for spine fractures but limited hip data.
- Selective Estrogen Receptor Modulators (SERMs): Raloxifene Hcl-60mg/d Increases BMD and reduces vertebral fractures. Suitable for women intolerant to bisphosphonates.
- Denosumab-60mg SC once in six months:
  Monoclonal antibody that inhibits osteoclast activity [9&15].

3. Anabolic Agents: Promote new bone formation.

Examples:

- Teriparatide-20mcg daily SC: Stimulates bone formation; reduces fractures significantly. Recommended for severe osteoporosis.
- Strontium Ranelate-2mg daily orally: Available in Europe, promotes bone formation while reducing resorption.
- Combination Therapy: Combining agents (e.g., bisphosphonates + HRT or calcium/vitamin D) [9]. Women with postmenopausal osteoporosis were divided in a 1:1:1 ratio to receive 20 µg teriparatide daily, 60 mg denosumab every 6 months, or both. The study demonstrated that therapy with combined teriparatide and denosumab significantly increased the lumbar spine BMD, femoral neck BMD, and total-hip BMD compared with teriparatide and denosumab alone [15].

4. Adjunct Therapies: Essential for bone health.

- Calcium-1200mg
- Vitamin D-800 IU

Considerations: Treatment choice depends on patient age, fracture risk, tolerability, and risk-benefit profile. Regular monitoring of BMD is crucial [9].

NON – PHARMACOLOGICAL THERAPY:

1. Lifestyle Modifications: Balanced diet, regular exercise, avoidance of smoking, alcohol, and fall-related injuries.

2. Dietary Recommendations: Calcium: 1200 mg/day (essential for bone health, muscle contraction, and nerve signaling).

- Protein: 1-1.2 g/kg/day to prevent bone and muscle loss.

- Healthy Foods: High intake of fruits, whole grains, and nuts; low intake of processed meat, candy, and saturated fats.

3. Supplements:

- Calcium: Use calcium citrate maleate for those with poor dietary habits or low gastric acid.

- Vitamin D: 60,000 IU of cholecalciferol every 1-2 months (common deficiency in India).

- Calcitriol: Reserved for renal impairment cases [16].

DISCUSSION:

Osteoporosis is a major public health issue globally, particularly affecting postmenopausal women due to hormonal changes that lead to a significant decline in bone mineral density (BMD). As the population ages, the burden of osteoporosis and related fractures is rising, contributing to increased morbidity, mortality, and healthcare costs. The disease is primarily characterized by fragile bones and an increased susceptibility to fractures, with significant impacts on quality of life.

The role of estrogen in bone metabolism, especially in postmenopausal women, is pivotal in the development of osteoporosis. Postmenopausal osteoporosis is primarily due to estrogen deficiency, which leads to an increased rate of bone turnover, characterized by excessive bone resorption and insufficient bone formation. This results in accelerated bone loss during the early years of menopause, placing women at a higher risk of fractures. As highlighted in the article, this loss of bone mass can be severe, with a notable decrease in trabecular bone density, which is more susceptible to fractures.

Pharmacological treatments for osteoporosis aim to either prevent bone resorption or stimulate bone formation. Hormone replacement therapy (HRT) has been the cornerstone of treatment for postmenopausal osteoporosis, though its use is increasingly selective due to concerns about long-term side effects.

CONCLUSION:

Osteoporosis remains a significant health challenge, particularly for postmenopausal women, due to the hormonal changes that lead to decreased bone density and increased fracture risk. Early diagnosis through BMD assessment and clinical evaluation of risk factors is crucial for preventing fractures and managing the disease. While pharmacological treatments, including HRT, bisphosphonates, and anabolic agents, have proven effective in reducing bone loss and fracture risk, lifestyle modifications, dietary changes, and supplements are equally important for supporting bone health. A comprehensive approach that includes both pharmacological and non-pharmacological interventions, tailored to individual patient needs, is essential for managing osteoporosis and improving patient outcomes. Regular monitoring and individualized treatment plans are key to reducing the impact of osteoporosis and enhancing the quality of life for affected individuals.

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