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POSTMENOPAUSAL OSTEOPOROSIS- AN UPDATED REVIEW

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ABSTRACT

Osteoporosis is a major growing public health problem with impact that crosses medical, social, and economic lines. Osteoporosis in older women is the 2nd most cause of death in America thus it is one of the essential area to be understand in medical science and need to update time to time. The objective of the present review is to update all aspect of osteoporosis in postmenopausal women, including current etiology, diagnostic methods, calculator of osteoporotic risk fators (FRAX), laboratory evaluation methods and biomarkers, drug therapy & newly approved drugs along with those under clinical trial.

INTRODUCTION: Osteoporosis is a skeletal disorder characterized by decrease in bone mineral density (BMD) and an associated deterioration of bone structure, causing bone fragility and increased risk of fracture. It simply means porous bones with low bone mass [1]. As the bones become more porous and fragile, the risk of fracture is greatly increased. The loss of bone occurs "silently" and progressively. Often there are no symptoms until the first fracture occurs.

The incidence of osteoporotic fractures in postmenopausal women increases exponentially with age. When menopause sets in many women experience physical and psychological changes. These changes are mostly due to the deficiency of female hormones, namely estrogen and progesterone [2].

As a consequence of the progressive aging of the population, the related problems are becoming major issues in many countries. Across the globe, the number of individuals with age 65 years and greater is expected to increase nearly fivefold between 1990 and 2050, from 323 million to 1.55 billion.

This trend alone could result in a 3.7 fold increase in the number of hip fractures worldwide from an estimated 1.7 million in 1999 to a projected 6.3 million in 2050 [3].

Approximately 10 million individuals over the age of 50 in U.S.A have osteoporosis of the hip. An additional 33.6 million individuals over the age of 50 have low bone mass or osteopenia of the hip and thus are at risk of developing osteoporosis at any site in the skeleton [4].

Many more women have osteoporotic fractures (1.4 million) than new strokes (373,000), heart attacks (345,000), or invasive breast cancer (213,000) combined, according to recent statistics (2004 to 2006).

Menopause and Osteoporosis: The increased rate of bone resorption immediately after menopause clearly indicates a hormonal influence on bone density in women. The most likely explanation for this increased resorption is the drop in ovarian estrogen production that accompanies menopause.

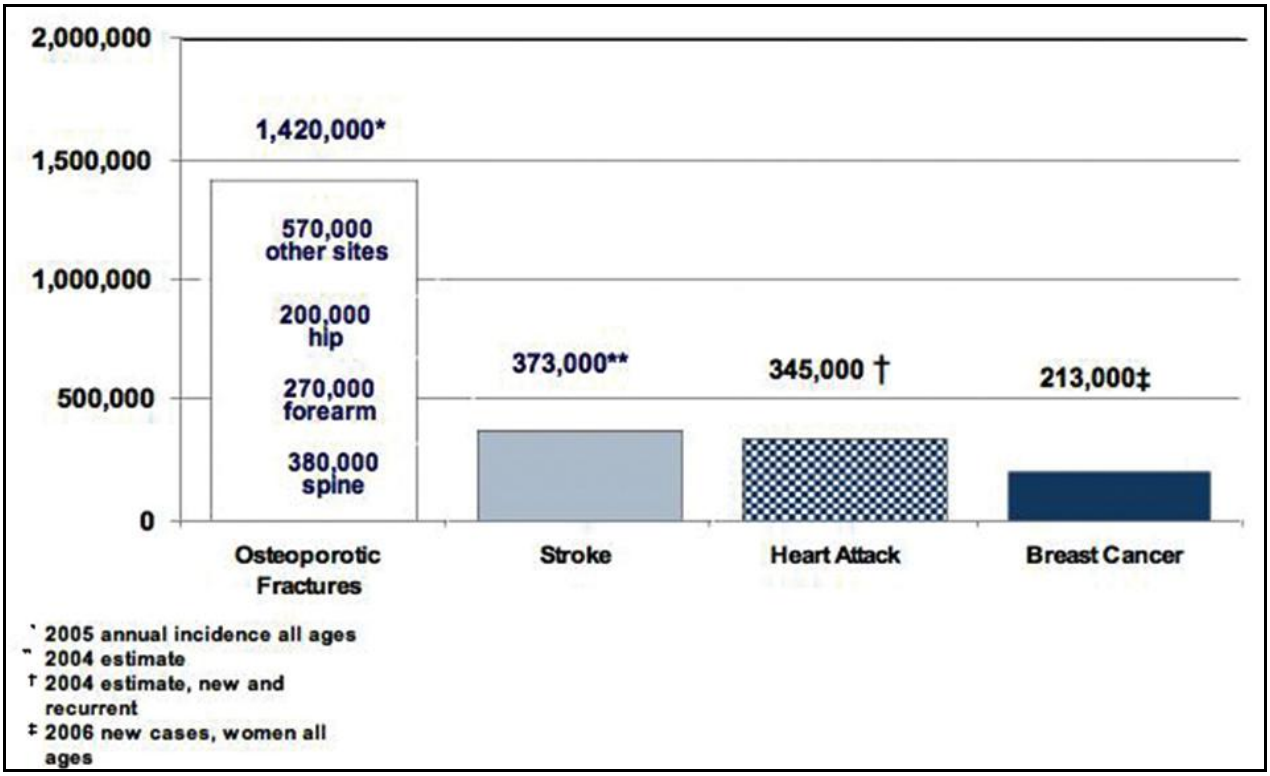

FIG. 1: COMPARATIVE INCIDENCES OF OSTEOPOROSIS-RELATED FRACTURES, NEW STROKES, HEART ATTACKS, AND BREAST CANCER IN WOMEN IN THE UNITED STATES, BASED ON RECENT STATISTICS (2004 TO 2006). Data from Burge *et al*, Rosamond *et al,* and American Cancer Society

Bone loss begins to accelerate about 2 to 3 years before the last menses, and this acceleration ends 3 to 4 years after menopause. For an interval of a few years around menopause, women lose 2% of bone annually. Afterward, bone loss slows to about 1% to 1.5% per year [6, 7]. A prospective, longitudinal study of white women reported BMD losses during this 5 to 7 year interval of 10.5% for the spine, 5.3% for the femoral neck, and 7.7% for the total body [6]. Although some of the decline can be attributed to age-related factors, lower estrogen levels were implicated as the cause for approximately two thirds of the bone loss.

Lower estrogen levels have also been significantly associated with increased fracture risk in older women (mean age, 75 years) [8]. Women experiencing menopause at or before age 40 either spontaneously or induced (eg, through bilateral oophorectomy, chemotherapy, or pelvic radiation therapy) are at greater risk of low BMD than other women of the same age who have not reached menopause [9]. However, by age 70, when fractures are more likely to occur, these women have the same risk for low BMD or fracture as women who reached menopause at the average age [11].

Pathophysiology:

Menopause and Bone Remodeling: Remodeling of the skeleton is crucial for maintaining its quality, and it is estimated that approximately 10% of the skeleton is renewed each year by this process. Remodelling maintains the mechanical integrity of the skeleton by replacing old bone with new. Bone resorption and bone formation occur at the same place, so that there is no change in the shape of the bone [12].

Post-menopausal osteoporosis is characterized by increased frequency of bone remodeling - i.e., in the skeletons of women suffering from this disease, an increased quantity of bone multi-cellular units is present. Increased frequency of bone multi-cellular unit activation in post-menopausal women leads to increased numbers of osteoclasts and resorption lacunae in the skeleton.

In post-menopausal osteoporosis, osteocalcin levels are increased, not because individual osteoblasts make more osteocalcin, but because of the increase in the number of bone forming osteoblasts. It is the increased frequency of activation sites, together with the decreased ability of individual osteoblasts to produce new bone, which is the reason bone mass decreases and bone strength is reduced. Most of the

drugs used today target the osteoclasts, to inhibit their activity and inhibiting further loss of bone, treatments with osteoclast inhibitors such as the bisphosphonates alendronate and risedronate can reduce fracture rates by 50%. Recently, intermittent administration of a 34-amino-acid fragment of human PTH (teriparatide) has been found to be a useful stimulator of bone formation in both trabecular and cortical bone. It causes increased bone mineral density and decreased incidence of vertebral and non-vertebral fractures [12].

Role of Estrogen Receptors: There are two different estrogen receptors (ER), the classic receptor, now called estrogen receptor ALPHA(ER-α), and the recently discovered estrogen receptor BETA(ER-β). ER-α is widely distributed and is expressed in both osteoblasts and osteoclasts. ER-β is expressed mainly in epithelial and mesenchymal tissues, including osteoblasts, but its expression in osteoclasts is more controversial. Stimulation of estrogen receptors in osteoblasts activates their anabolic activities and decreases the pathway by which osteoblasts can activate osteoclasts.

Activation of estrogen receptors in osteoclast progenitor cells decreases osteoclast formation, and activation of estrogen receptors in terminally differentiated osteoclasts inhibits their bone-resorbing activity. The estrogen receptors can bind not only estrogen, but also the so-called selective estrogen-receptor modulators (SERMs).These compounds activate estrogen receptors in bone, but act as antagonists in other organs, such as the breast and uterus. Raloxifene, is currently used for the treatment of osteoporosis. Like estrogen, the compound mainly acts as an inhibitor of bone resorption [12].

Diagnosis: Osteoporosis is a silent disease, because bone loss occurs without symptoms. Often, the first indication of the disease is a fracture. A fragility fracture results from forces that would not normally cause a fracture, such as a hip or wrist fracture from falling from standing height or a vertebral compression fracture.

Bone Mineral Density Test: Postmenopausal osteoporosis is usually diagnosed by measuring bone mineral density (BMD), the amount of bony tissue found in a given volume of bone, expressed as grams of mineral per area or volume.

Bone mineral density (BMD) criteria were developed by the World Health Organization (WHO) from epidemiologic data that describe the normal distribution of BMD in a young healthy reference population. Osteoporosis is diagnosed when the BMD at the spine, hip, or wrist is 2.5 or more standard deviations (SD) below the reference mean. Low bone density or mass (sometimes referred to as osteopenia) is diagnosed when BMD is between 1.0–2.5 SD below the reference mean [13].

TABLE 1: WORLD HEALTH ORGANIZATION CRITERIA FOR CLASSIFICATION OF OSTEOPENIA AND OSTEOPOROSIS

Category	T-Score
Normal	-1.0 or above
Ostepenia	Between -1.0 and -2.5
Osteoporosis	-2.5 or below

To standardize values from different bone densitometry tests, results are reported as either a Z-score or a T-score, with both expressed as standard deviation (SD) units.

- A T-score is useful to express BMD in a postmenopausal population and is calculated by comparing current BMD to the mean peak BMD of a normal, young adult population of the same gender. The reference database is white (non race-adjusted) women, although this approach is not universally agreed upon.

- For premenopausal women under age 50, use of Z-scores is the preferred manner of expressing BMD.

- A Z-score is based on the difference between the persons BMD and the mean BMD of a reference population of the same gender, age, and ethnicity [13].

BMD Measurement Techniques: Screening tests for osteoporosis must be accurate, sensitive, and easily accessible. Dual-energy x-ray absorptiometry (DXA) is recognized as the reference method to measure bone mineral density (BMD) accurately and reproducibly.

TABLE 2: VARIOUS BMD MEASUREMENT TECHNIQUES

Technique	Sites	Unit of measure	Uses
DXA	PA spine, lateral spine, proximal femur) total body, forearm, heel, phalanges	Areal density (g/cm^2)	Diagnosis and monitoring
QCT	Spine	Volumetric density (g/cm^3)	Diagnosis and monitoring
pQCT	Forearm, hip	Volumetric density (g/cm^3)	Risk assessment
QUS	Heel, forearm, tibia, phalanges metatarsals	SOS, BUA	Risk assessment
RA	Phalanges	Volumetric den(arbitrary units) Sity	Risk assessment

PA= posteroanterior; pQCT = peripheral quantitative computed tomography; QCT= quantitative computed tomography; QUS = quantitative ultrasonometry; RA = radiographic *BUA= broadband ultrasound attenuation; DXA= dual x-ray absorptiometry; PA absorptiometry; SOS = speed of sound [14]

FRAX- The FRAX® tool has been developed by WHO to calculate the 10-year probability of a hip fracture and the 10-year probability of a major osteoporotic fracture (vertebral, hip, forearm or humerus fracture) taking into account femoral neck for several countries, including the UK.

The FRAX® tool has not been validated in patients currently or previously treated with pharmacotherapy for osteoporosis. In such patients, clinical judgment must be exercised in interpreting FRAX® scores.

Assessment by the FRAX tool should be undertaken in:

- All postmenopausal women without fracture but with a WHO risk factor or a BMI < 19kg/m².
- Men aged 50 years or more (with or without fracture) but with a WHO risk factor or a BMI < 19kg/m²
- China, France, Italy, Japan, Spain, Sweden, Turkey, UK and the USA
- The 10-year probability of hip fracture or of a major osteoporotic fracture clinical spine, hip, forearm and humerus fracture [15]

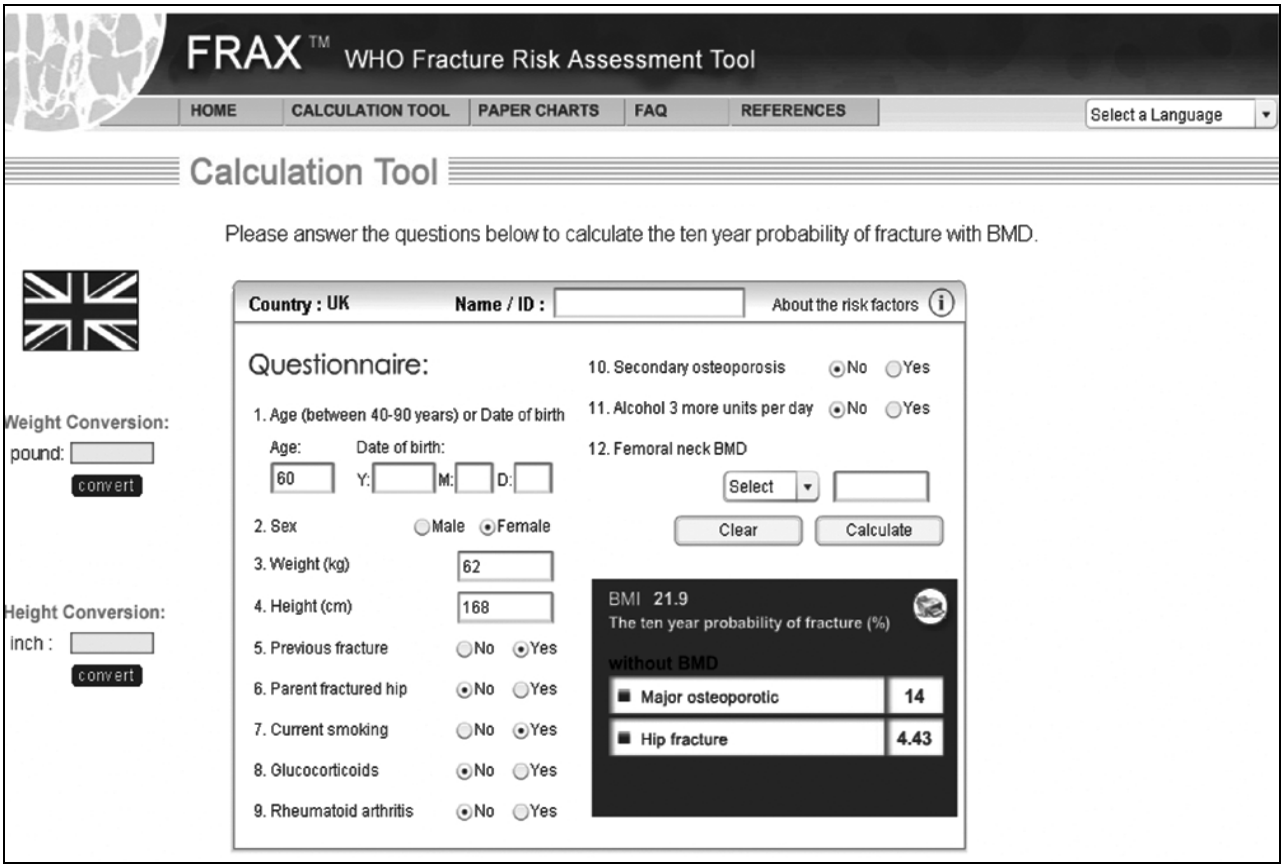

FIG. 2: SCREEN SHOWING THE INPUT AND OUTPUT OF THE FRACTURE RISK ASSESSMENT MODEL FOR THE UNITED KINGDOM

Clinical Risk Factor: Number of risk factors has been included in the WHO 10-year fracture risk model. This set of risk factors increases risk independently of BMD and can be combined with BMD measurements and used to assess an individual patient's risk of future fracture [16].

TABLE 3: RISK FACTORS FOR OSTEOPOROTIC FRACTURE USED IN FRAX

Risk Factors Included in the WHO Fracture Risk Assessment Model
• Current age
• Rheumatoid arthritis
• Gender
• Secondary osteoporosis
• A prior osteoporotic fracture (including morphometric vertebral fracture)
• Parental history of hip fracture
• Femoral neck BMD
• Current smoking
• Low body mass index (kg/m2)
• Alcohol intake (3 or more drinks/d)
• Oral glucocorticoids ≥5 mg/d of prednisone for ≥3 mo (ever)

Evaluation: It is important to evaluate fracture risk, to rule out secondary causes of osteoporosis, to identify modifiable risk factors, and to determine appropriate candidates for pharmacologic therapy.

Physical Examination: Along with medical history and physical examination, secondary cause of the osteoporosis and fragility must be evaluated by using WHO FRAX risk factors (see table) and are used with guidelines for treatment thresholds, this is very helpful in identifying candidates for pharmacotherapy [17].

After menopause, a woman risk for falls should be assessed. Clinical factors related to an increased risk of falls include the following:

- A history of falls, fainting, or loss of consciousness
- Muscle weakness
- Dizziness, coordination, or balance problems
- Difficulty standing or walking
- Arthritis of the lower extremities
- Neuropathy of the lower extremities
- Impaired vision

The risk of falls is also increased by use of medications that affect balance and coordination (e.g., sedatives, narcotic analgesics, anticholinergics, antihypertensives) or by use of multiple medications. [17].

Bone Turnover Markers: Bone markers can indicate either osteoclastic bone resorption i.e. breakdown products of type I collagen in bone: N-telopeptides, C-telopeptides, deoxypyridinoline or osteoblast functioning i.e., bone matrix synthesis: bone-specific alkaline phosphatase, procollagen type I N-terminal propeptide, osteocalcin). Most bone turnover markers vary greatly from day to day, are affected by food intake and time of day, and lack assay standardization, limiting their clinical utility. In some cases, persistently elevated bone turnover markers in the face of antiresorptive therapy may alert the clinician to nonadherence to therapy, poor absorption of medication, or other secondary causes of osteoporosis. Biochemical markers of bone turnover can be measured in serum or urine [17].

Routine Laboratory Tests: Routine tests for patients with low bone mass include a complete blood cell count, serum calcium, phosphate, creatinine, thyroid-stimulating hormone, alkaline phosphatase, and albumin.

Tests for serum 25-hydroxyvitamin D [25(OH) D] and 24-hour urinary calcium excretion may be useful to detect patients with poor calcium and vitamin D nutrition as well as those with hypercalciuria. Special tests that may be appropriate in some clinical circumstances include 24-hour urine free cortisol, serum protein electrophoresis, tissue transglutaminase antibody, and intact parathyroid hormone (PTH) [17].

TABLE 4: ROUTINE LABORATORY TESTS FOR OSTEOPOROSIS EVALUATION

Test	Result of Diagnosis	Cause
Complete Blood cell Count	Anemia	Multiple Myeloma
Serum Calcium	Elevated	Hyperparathyroidism
	Low	Vit. D deficiency GI Mal-absorption
Serum Phosphate	Elevated	Renal Failure
	Low	Hyperparathyroidism
Serum 25-Hydroxyvitamin-D	Low	GI Mal-absorption, Celiac Disease
Serum Alkaline Phosphatase	Elevated	Vit. D deficiency, Liver Disease, GI Mal-absoption, Pagets Disease, Hyperparathyroidism
Urinary Calcium Excretion	Elevated	Renal Calcium Leak, multiple myeloma, metastatic cancer, Hyperparathyroidism
	Low	GI Mal-absorption, Inadequate intake of Calcium, & Vit. D
TSH	High	Hypothyroidism
	Low	Hyperthyroidism
Serum Protein Electrophoresis	Monoclonal Band	Multiple myeloma
Tissue Trans-glutaminase Antibody	Elevated	Celiac Disease
Creatinine	Elevated	Renal osteodystrophy

Treatment: As per the National Osteoporosis Foundation Clinician's Guide 2010 to Prevention and Treatment of Osteoporosis recommendations, pharmacologic treatment for postmenopausal women with the following:

- A hip or vertebral (clinical or morphometric) fracture
- T-score ≤ -2.5 at the femoral neck or spine after appropriate evaluation to exclude secondary causes
- Low bone mass (T-score between -1.0 and -2.5 at the femoral neck or spine) and a 10-year probability of a hip fracture ≥ 3% or a 10-year probability of a major osteoporosis-related fracture ≥ 20% based on the US-adapted WHO algorithm [16].

Several pharmacologic options are available for osteoporosis therapy, including bisphosphonates, the selective estrogen receptor modulator (SERM; also known as estrogen agonist/ antagonist) raloxifene, PTH, estrogens, and calcitonin.

Bisphosphonates: Bisphosphonates are the most widely used drugs for treatment of osteoporosis. Clinical trials have showed that bisphosphonates will increase BMD at hip and spine in a dose dependent manner in both younger and post menopausal women and reduces the risk of vertebral fractures by 40-70% and hip fractures by 20-35%. Bisphosphonates are available as daily and intermittent dosage regimen oral formulation and also as IV injections [18].

Classes of Biphoshonates includes-

- Nitrogen Containing Bisphosphonates: (eg. Pamidronate, alendronate, risedronate)
- Non-Nitrogen Containing Bisphosphonates: (eg. etidronate, clodronate)
- Intravenous Bisphosphonates: (eg. Zoledronic Acid, 5mg given annually)

Newer Bisphosphonates: Three oral bisphosphonates have FDA approval for treating and preventing osteoporosis: alendronate (Fosamax, Merck), risedronate (Actonel, Procter & Gamble/Sanofi-Aventis) and ibandronate (Boniva, Roche) given on daily basis. Alendronate and risedronate are also available in once weekly oral formulations, and ibandronate is available in a once monthly oral formulation. Injectable ibandronate is available for quarterly administration [19-21].

Selective Estrogen Receptor Modulators: These non steroidal agents of various chemical structures act as estrogen agonists and/or antagonists. The only SERM raloxifene (marketed as Evista oral tablets) is U.S.

Government approved (although several are in clinical development) for the prevention and treatment of osteoporosis at a dose of 60 mg/day. Raloxifene has beneficial effects on BMD, and it decreases bone turnover as assessed by biochemical markers [17].

Newer SERM:

- **Bazedoxifene:** This SERM has prevented bone loss and decreased bone turnover without stimulating the endometrium in healthy postmenopausal women with normal or low BMD. The tolerability profile of bazedoxifene treatment was similar to that of raloxifene. bazedoxifene 20 or 40 mg/day reduced the incidence of vertebral fracture by 42% and 37%, respectively,

- **Lasofoxifene:** Another SERM that increased lumbar spine BMD and reduced bone markers modestly more than did raloxifene in young postmenopausal women without osteoporosis. lasofoxifene in daily doses of 0.25 mg and 0.5 mg significantly reduced vertebral fracture Risk by 31% and 42% respectively.

Estrogens: Systemic estrogen products (estrogen+ progestogen [EPT] for women with a uterus or ET for women without a uterus) are government approved in the United States and Canada for prevention, but not treatment, of postmenopausal osteoporosis [17].

Parathyroid hormone: PTH and their analogues given by subcutaneous injection once daily are anabolic agents that directly stimulate osteoblastic bone formation, resulting in substantial increases in trabecular bone density and connectivity in women with postmenopausal osteoporosis. Eg.Teriparatide marketed as Forteo (Human r-PTH 1-34) [17].

Calcitonin: Calcitonin is an inhibitor of bone resorption. Approved as a nasal spray (Miacalcin Nasal Spray, Fortical Nasal Spray) and a subcutaneous injection (marketed as Miacalcin Injection). The efficacy of calcitonin has not been observed in early postmenopausal women. Thus, product labeling recommends its use only in women with osteoporosis who are at least 5 years beyond menopause [22].

Tibolone: Tibolone is a tissue-specific, estrogen-like agent that may prevent bone loss and reduce menopausal symptoms but it does not stimulate breast or uterine tissue**.** Tibolone reduced the risk of vertebral and nonvertebral fracture, breast cancer, and possibly colon cancer, but increased the risk of stroke in older postmenopausal women with osteoporosis. Thus tibolone is not approved in US and Canada [17].

Strontium ranelate: strontium ranelate approved and marketed as protelos, dosing involves dissolving 2 grams of strontium ranelate in water and drinking it before bedtime. Strontium ranelate reduces the risk of both spine and non-vertebral fractures, but the mechanism is unclear. Incorporation of strontium into the crystal structure replacing calcium may be part of its mechanism of effect. Bone density in patients taking strontium ranelate will be artifactually increased by the effects of the higher atomic number of strontium ranelate as compared with calcium [17].

Combination therapies: Following combinations are recommended and so approved-

- Combined alendronate and ET- BMD improvements in the spine and hip were significantly greater (8.3%) than results for either agent alone (6.0%) [23].

- Combined risedronate and ET/ EPT shown favorable, modest, BMD effects compared with either agent alone [24].

- Combining an anabolic agent such as teriparatide with an antiresorptive agent has been considered. Significant increases in BMD occurred in an RCT when teriparatide was added to ongoing ET [25].

- Combining PTH 1-84 and alendronate, the BMD response was less than that seen with PTH alone [26].

Calcium and Vitamin-D: Providing adequate daily calcium and vitamin D is a safe and inexpensive way to help reduce fracture risk. Lifelong adequate calcium intake is necessary for the acquisition of peak bone mass and subsequent maintenance of bone health. The skeleton contains 99 percent of the body's calcium

stores; when the exogenous supply is inadequate, bone tissue is resorbed from the skeleton to maintain serum calcium at a constant level. Vitamin D plays a major role in calcium absorption, bone health, muscle performance, balance and risk of falling. An adequate intake of both calcium and vitamin D is important for bone health and is recognized as an important component of any osteoporosis prescription-drug regimen.

Most widely accepted guidelines for osteoporosis support the published recommendations for total daily calcium consumption from the National Osteoporosis Foundation (NOF) [16], the National Institutes of Health [27], the National Academy of Sciences (NAS) [28], or Osteoporosis Canada [29]. Recommendations for perimenopausal and postmenopausal women are presented in **Table 5**.

TABLE 5: DAILY DOSE OF ELEMENTAL DIET OF CALCIUM AND VITAMIN-D RECOMMENDED BY VARIOUS NATIONAL GUIDELINES

National Institute of Health	Calcium/day	Vitamin D/day
Premenopausal women ages 25-50	1000 mg	2,000 IU
Postmenopausal women younger than age 65 and using estrogen therapy	1000 mg	
Postmenopausal women not using estrogen therapy	1500 mg	
All women age 65 and older	1500 mg	
National Academy of Sciences		
Age 31-50	1000 mg	
Age 51 and older	1200 mg	400 to 600IU
Osteoporosis Canada women over age 50	1500 mg	400 to 800 IU
National Osteoporosis Foundation		
Women age 50 and over	1200 mg	800 to 1,000 IU
Osteoporosis Canada		
Women over age 50	1500 mg	800 and 2000 IU

Other Dietary Supplements: Magnesium- A necessary supplement for the protection of bone health and/or for absorption of calcium. Magnesium is plentiful in foods such as Green leafy vegetables, unpolished grains, and nuts. The total intake of magnesium is generally dependent on the total caloric intake; magnesium intake tends to fall after age 70. The RDA for magnesium is 320 mg/day in women age 31 and older [30].

Vitamin K: The predominant form of vitamin K is vitamin K1 (phylloquinone), found in green leafy vegetables, The average dietary intake of vitamin K is approximately 340 Kg/day. Supplementation with vitamin K1 (1 mg/d) in conjunction with calcium, magnesium, zinc, and vitamin D appeared to be associated with beneficial effects on bone turnover and bone density at the femoral neck [31].

Isoflavones: "Natural" estrogens are promoted to prevent bone loss. Isoflavones are a class of phytoestrogens found in rich supply in soybeans, soy products, and red clover. No conclusive data, however, support the use of these agents for increasing bone density or decreasing fracture risk [32].

DISCUSSION AND CONCLUSION: Many women experiences physical and physiological changes after menopausal state mostly due to the deficiency of female hormones, namely estrogen and progesterone. The osteoporosis can be diagnosed using techniques like DXA, QUC, QCT, pQCT, RA for the measurement of BMD. WHO FRAX calculator is employed as a recent tool for evaluation & diagnosis of risk factors of postmenopausal osteoporosis.

Number of bone turn over markers are found in patient with menopausal osteoporosis such as bone matrix synthesis substances like bone-specific alkaline phosphatase, procollagen type- I, N terminal propeptide, osteocalcin or breakdown products of type- I collagen in bone: N telopeptides, C-telopeptides, deoxypyridinoline. These biochemical markers of bone turnover can be measured in serum or urine.

Treatments of postmenopausal osteoporosis are made in conjunction with patient's age, BMD results, history of previous fractures, and high risk factor for bone loss. Non pharmacological approaches should be studied to manage the occurrence of postmenopausal osteoporosis.

Future research priorities include determination of optimal duration of treatment, evaluation of strategies directed at improving management of women with osteoporotic fractures, and the completion of head to head trials of treatments with clinically relevant outcomes of clinical fracture and quality of life. A focus on early diagnosis and treatment of osteoporosis with selection of the most suitable agent for each individual will contribute to the improved health and well-being of postmenopausal women.

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