REVIEW ARTICLE

Postmenopausal Osteoporosis: Menopause Hormone Therapy and Selective Estrogen Receptor Modulators

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Abstract

Introduction Osteoporosis is a debilitating silent disease with a huge socio-economic impact. Prevention strategies and early detection of osteoporosis need to be carried out in every health care unit to substantially reduce the fracture rates. Indian studies have indicated a knowledge gap on diagnosis and management of osteoporosis amongst medical professionals and consumers.

Areas Covered This article reviews the evidences available on searches from PubMed and The National Library of Medicine, author's opinions based on clinical experience. There is a need for escalating the efforts to bridge the knowledge gap regarding various aspects of osteoporosis amongst professionals and consumers. Three indications for postmenopausal hormone therapy (HT), which have constantly withstood the test of time, are symptom relief, urogenital atrophy, and bone health. This article specifically focuses on management of postmenopausal osteoporosis by HT alone or in combinations.

Expert Opinion Early menopause is within 10 years of menopause and late menopause is considered beyond 10 years of menopause. HT is a cost-effective therapy in the early post menopause especially in symptomatic women at risk for osteoporosis unless contraindicated. HT prevents all osteoporotic fractures even in low-risk population. All HT preparations including low dose and non-oral routes of estrogen are effective for bone health. The bone protective effect lasts while on HT. Extended use of HT in women after 10 years of menopause with reduced bone mass is an option after detailed counselling of the risk benefit analysis compared with the other available therapies for osteoporosis. The primary therapy to prevent bone loss in women with premature menopause and secondary amenorrhea is HT. HT work up and annual follow-up is essential before prescribing HT.

Keywords Postmenopausal osteoporosis · Hormone therapy · Selective estrogen receptor modulators · Individualize therapy

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Introduction

The most prevalent systemic skeletal disease associated with ageing and estrogen deficiency is osteoporosis. Refer to Fig. 1, osteoporosis presents with decreased bone mineral density and there are changes in structure and strength of bone tissue, resulting in high risk for osteoporotic or fragility fracture [1]. Fragility fracture is defined as a fracture due to fall from a standing height. Osteoporosis is a silent disease and its first symptom—osteoporotic fracture is devastating for the patient and the caregivers. At and beyond 50 years of age, there is 40% lifetime risk for osteoporotic fracture. Women have 2–4 times greater risk for an osteoporotic fracture than in men [2]. In simple terms 1 out of 2 women and 1 out of 5 men older than 50 years will suffer from osteoporotic fractures [3]. Hip fracture is more frequent than the
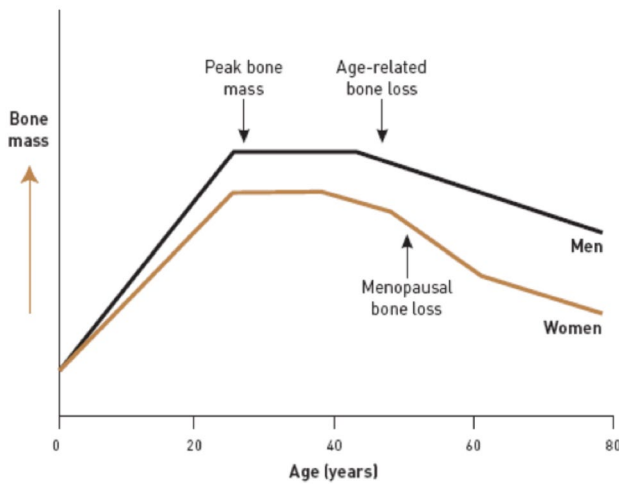
Fig. 1 Graphical representaion of menopause and age-related bone loss in men and women

combined risk of breast, uterus and cervical malignancy. Mortality rate is 12–20% within 1 year of hip fracture, more than 50% becomes dependent and more than 30% are left with permanent disability [4]. With spinal fracture there is shortening of height, crowding of internal organs, back pain, kyphosis, prolonged disability, and increased mortality [5].

There is rapid increase in number of elderly women in Asia, Latin America, the Middle East, and Africa. It has been projected that these parts of world will account for more than 70% of the estimated 6.26 million fractures which is expected in the year 2050 [6]. The prevalence of postmenopausal osteoporosis as reported in Indian studies has a wide range of 8–80% [7]. There is insufficient population-based epidemiological data on fractures. Indian data from hospital regarding fractures in hip indicate that they are common in women between 60 and 70 years of age. A study from North India, Rohtak district reported rate of hip fracture as 159 per 1 lac women above age of 50 and this hospital-based study has being used to define interventional thresholds in Fracture Risk Assessment Tool (FRAX) for India [8]. Risk of vertebral fracture in Indians is not very different from the Western and other Asian populations and tends to be lesser in overweight population [9]. More than 50 million people in India had low bone mass [1]. Age wise stratification of the risk shows more than 40% prevalence of low bone mass from the age of 40 years, which increases by more than 62% by age 60 years and 80% by the age of 65 years in women [7]. In addition, when compared to Caucasians, Indians suffer from osteoporotic fractures 10–20 years earlier than them [11, 12].

Considering the magnitude of the problem and its socio-economic impact, all health care units should work upon prevention and early detection of osteoporosis. Indian studies have indicated a knowledge gap in diagnosing and managing osteoporosis amongst medical professionals and consumers [13, 14]. These studies emphasize the need for escalating the efforts to bridge the gap regarding various aspects of osteoporosis amongst professionals. In continuum, there is a need to work on awareness campaigns on prevention and management of osteoporosis at a community level.

Estrogen and Bone

Postmenopausal women experience primary osteoporosis; estrogen deficiency is the leading cause of increased risk (Fig. 2). In 1882, Bruns first demonstrated that proximal femur fracture was more common in women [15]. Later in 1940, Albright et al. noted that vertebral fractures were common amongst women with surgical menopause [16]. An association and hypothesis were laid, and today, there is enough evidence to establish the association between estrogen and bone health.

Estrogen-deficient states, such as menopause, premature menopause, persistent anovulation, and amenorrhea,
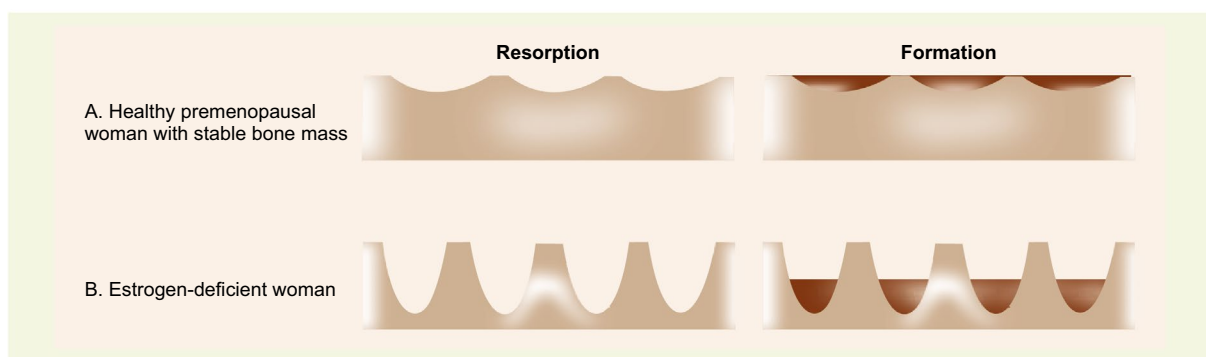

Fig. 2 A Pictorial representation of resorption and formation with a stable bone mass. **B** Increased resorption in estrogen deficiency leading to decreased bone mass

and medications such as gonadotropin-releasing hormone agonists are associated with bone loss [17, 18]. Aromatase inhibitors (AIs) used in treatment of hormone-responsive breast cancer, effectively block estradiol biosynthesis in peripheral tissues [19]. AIs suppress circulating estrogen levels beyond those observed after natural menopause, and rates of AI-associated bone loss exceed the bone mineral density (BMD) loss rate after menopause by more than two-fold [20]. This has been observed as increased fracture rates in clinical trials comparing AIs with placebo in women with early breast cancer [21].

The acceptance of the entity postmenopausal osteoporosis (PMO) indicates the role of ovarian steroid hormones in metabolism of bone. At menopause, the rate of bone loss is accelerated in the background of the slow rate of cortical bone loss occurring with the ageing process. There is decrease in the trabecular bone width after menopause, followed by decrease in thickness of cortical bone beyond age 70.

Estrogen deficiency leads to increased bone turnover marked by accelerated osteoclast-mediated bone reabsorption and deficient bone formation, resulting in decreased bone mass [22]. Rate of bone loss is 1–5% per year due to declining estrogen levels in the first 5–7 years of menopause [23]. Women's response to the declining ovarian steroid levels is labelled as fast losers [> 3% change in BMD per year] and average losers (< 3% change in BMD per year) [24]. The collagen matrix is responsible for the strength of bone which constitutes 90% of the organic matrix of bone. There is decline in collagen content of bone with ageing but it decreases significantly more in the postmenopausal period owing to estrogen deficiency [25].

Cortical bone collagen levels correlate with both estradiol levels and BMD [25]. Cummings et al. observed that the BMD is higher for serum estradiol greater than 10 pg/ml and lower for the same being < 5 pg/ml. For serum estradiol less than 5 pg/ml, fractures are increased by eight times [26].

It is well-known that bone resorption is very fast in the initial 3–4 years of menopause, so consideration should be given to begin hormone therapy soon after menopause, given the window of opportunity. This is the period during which the response to treatment can be maximum, as stopping resorption leads to instant filling and remodelling, thereby increasing bone formation and hence a significant increase in BMD [7].

Hormone Therapy

It includes many hormonal products—estrogens, progestins, androgens, tissue-selective estrogen complex as tibolone and selective estrogen receptor modulator. They can be given by different routes with different side effect profile. The risks and benefits vary for different age groups.

The terminology used in this review for hormone therapy is—HT—hormone therapy; MHT—menopausal hormone therapy; HRT—hormone replacement therapy; ET—estrogen therapy; EPT estrogen–progesterone therapy; and AT-androgen therapy.

Role in Postmenopausal Osteoporosis

Based on the evidences regarding effectiveness, safety and cost, standard MHT should be given as one of the first-line therapies for preventing and treating postmenopausal fractures women younger than 60 years unless there is a contraindication [7].

On the other hand, as per available evidences, MHT initiation after 60 years for prevention of fracture is not recommended. However, in women already on MHT, its continuation beyond age of 60 should be considered for possible beneficial long-term compared to other non-hormonal therapies [7].

Using a high dose of HT/ET for initial 6 months followed by reducing the dose in subsequent years will treat bone loss effectively in postmenopausal women by rapidly reducing bone resorption in initial estrogen deficiency phase.

HT and ET were commonly used in the last 30 years, but their use declined following the publication of the Women's Health Initiative (WHI) study in 2001.

Evidence for Hormone Therapy in Osteoporosis

Albright's original observational open-labelled studies demonstrated that estrogen-treated osteoporotic women maintained their height, unlike untreated women [27].

Estrogen was being used for 30 years as hormone therapy in postmenopausal osteoporosis prior to the 1st release of Women's Health Initiative (WHI) study with evidence backing its use in all age groups. A lower risk of fractures in hip was demonstrated in post-menopausal women with higher circulating levels of 17-beta estradiol in the study of Osteoporotic Fractures [26].

Dual-energy X-ray absorptiometry (DXA) showed an increase in BMD of hip and spine over a period of 2 years in a double-blind study named The Postmenopausal Estrogen Progestin Intervention study (PEPI); and a decline in biochemical markers indicating that HT reduces the rate of remodelling. It also demonstrated that there was a bone loss when HT was discontinued [28].

The meta-analysis done on observational and randomized controlled trials further supports estrogen replacement

therapy to be used as first line treatment to prevent and treat fractures due to bone loss. It showed that postmenopausal HT increases bone mass by decreasing turnover of bone thereby reducing osteoporotic fracture rate and also extra-skeletal beneficial effects by reducing 30–50% and 15–20% chances of coronary heart disease (CHD) and cerebrovascular accidents, respectively. This positive effect on bone was also seen when ET was started in late menopause. HT when initiated early in the phase of transition to menopause showed the most significant benefit [29].

The best data to date on HT is the significant reduction of 24–39% in osteoporotic fracture, as seen from WHI, the most prominent landmark randomized trial. There was significant decline in the incidence of fractures in women on long-term HT (5.6 years of combined HT: absolute rate was 86 per thousand, 95% confidence interval being 79–84; after 7.1 year usage of estrogen only HT: absolute rate was 102 per one thousand, 95% confidence interval being 91–112). The only clinical outcome where benefit was seen substantially from HT was decrease in risk of fracture [30].

This is in tune with the observational trials and meta-analysis by Torgerson et al., where use of HT indicated a significant reduction in all fragility fractures [31].

The first randomized trial which demonstrated a decline in the incidence of all osteoporotic-related fractures in unselected population compared to placebo is the WHI. No difference in effect was found when stratification of women was done by body mass index (BMI), age and time since menopause. It also showed that HT started in older women could prevent osteoporosis at different selected sites. No significant reduction was found in fracture after treatment with HT for postmenopausal women with CHD in The HERS (Heart and Estrogen/progestin Replacement) trial.

Cochrane Review 2012 has shown a significant fall in the risk of fractures in women using continuous combined HT or estrogen-only HT when followed up over near 8 years. Despite HT being considered sufficient for preventing osteoporosis in postmenopausal women, it has been recommended only for those women with significant risk, where non-estrogen treatment seems unsuitable [32].

A fall in use of estrogen therapy was seen for a decade after 2002 when WHI result was released in hurry. WHI data were re-analyzed which mentioned that HT within 10 years of menopause was safe unless contraindicated and this gave the theory of the "window of opportunity".

Compared to placebo MHT was shown to decrease fracture risk in the combined WHI trials, irrespective of FRAX probability and history of falls in postmenopausal women [33].

A systematic review which included the WHI results, randomized controlled trials (RCT) and clinical trials of duration at least 1 year looked at different aspects of hormone therapy and bone. BMD measurement showed similar results when comparing prevention and treatment trials, opposed and unopposed HT, oral and transdermal estrogen and various types of progestogens [34].

Low-Dose HT

HT showed a dose-dependent effect on bone. Post WHI, the thought was to lose an effective dose of HT for a minimum duration. This led to research on low-dose HT(LD-HT) and ultra-dose HT based on the concept that the required dose of estrogen to protect bone is much lower than previously thought. 1 mg Estradiol, 0.45 mg conjugated equine estrogen (CEE), or 25 µg estradiol via transdermal patch are protective, and some evidence exists for even lower doses. Ultralow doses of oral CEE 0.3 mg, 17 E estradiol 0.5 mg and 14 ug estradiol transdermal route have been studied in both early (mean age 51–52) and late postmenopausal (mean age 67–74) with significant increases in BMD in both populations [35]. Furthermore, older postmenopausal women may achieve similar skeletal effects with lower estrogen doses than younger women. Lees et al. demonstrated that 1 mg estradiol in women over 58 years achieved the same increase in bone density as 2 mg in those under 51 years.

The efficacy of LD-HT to prevent osteoporosis has been assessed in several studies. It can reduce turnover rate of bone by 30% approximately thereby increasing bone density. Younger postmenopausal women (age 50–53 years, 3–5 years after menopause) have also been benefitted by LD-HT in preventing bone loss in addition to other menopausal symptoms, such as hot flushes, mood change and sexual dysfunction. LD-HT has added benefit of personalizing the doses as per each patients' needs. The first one large randomized placebo control trial which evaluated BMD after lower doses of CEE alone or in combination with low dose of medroxyprogesterone acetate (MPA) was the women's HOPE (Health, Osteoporosis, Progestin, Estrogen) study. This study demonstrated lower doses of CEE (0.45 mg and 0.3 mg per day), with or without a low dose of MPA (1.5 mg per day) helped in preventing BMD loss in hip and spine. It reduced turnover of bone in early postmenopausal women in addition to relieving vaginal atrophy, vasomotor symptoms, endometrial hyperplasia and had better bleeding profiles [35].

Tibolone

Tibolone is a synthetic steroid which belongs to selective tissue estrogenic activity regulator (STEAR) group. It has estrogenic, androgenic and progestogenic effects. It reduces osteoclastic activity in bone and thus inhibits bone resorption which is estrogenic effect. It has been

approved to prevent osteoporosis and to treat symptoms of menopause 1 year after amenorrhea. The LIFT study, which was a trial by Cummings et al. in 2008, to evaluate tibolone in treatment of osteoporosis in older menopausal women having mean age of 68 years examined the use of 1.25 mg of tibolone. A significant decline in both fractures of vertebra and non-vertebral sites was observed in comparison with placebo, but an increase in rate of stroke was also found [36].

Selective Estrogen Receptor Modulators

SERMs are Selective Estrogen Receptor Modulators which lack steroid structure of estrogen but they can act at estrogen receptor as agonist or antagonist in different tissues. Initially SERMs were developed to prevent and treat breast cancer, such as tamoxifen and raloxifene, but later they were found to conserve bone mass. Tamoxifen had been used as adjuvant in treatment and prevention (in high-risk women) of breast cancer for about last 30 years. While tamoxifen had a significant bone-sparing effect, its unwanted effects were high risk of endometrial malignancy, pulmonary embolism, deep-vein thrombosis, stroke and cataracts. Therefore, it's not used to prevent or treat osteoporosis in menopausal women [37].

60 mg raloxifene per day helps to preserve and improve the density of bone at spine (2.6%) and hip (2.1%) at 4 years of use and it also reduces risk of invasive breast cancer by 76%. It lacks efficacy in reducing hip fracture. Risk reduction of new fracture in vertebra is seen by the tune of 69% in postmenopausal osteoporotic women and by 47% in postmenopausal women with osteopenia over 3 years [38]. While raloxifene can prevent and treat osteoporosis especially in women having increased risk of breast cancer, its side effects are increase in risk of venous thromboembolism (VTE) as with estrogen, hot flushes being more likely in perimenopausal time and cramps in legs.

Bazedoxifene

Bazedoxifene is one SERM which was synthesized to improve skeletal symptoms and lipid profile specifically without having any effect on hot flushes. The first FDA approved combination of conjugated estrogen and estrogen agonist/antagonist is CE/BZA (conjugated estrogen and bazedoxifene) which relieves vasomotor symptoms in addition to preventing osteoporosis. This combination of CE/BZA is called tissue selective estrogen complex (TSEC) that is not available in India [40].

Combination Therapy with Hormone Therapy

Not all but some studies have shown combination of estrogen plus bisphosphonates being more effective in increasing BMD than either drug alone. Addition of calcium supplement to ET was found in a study to increase BMD of spine by 2% and that of femoral neck by 1.5% when compared to ET/HT alone. When alendronate was combined with estradiol/norethisterone acetate, no increase in BMD of hip was found when compared to either medication alone [41]. Alendronate, risedronate and calcitriol can be combined with 0.625 mg CEE. Combining two agents have shown 2% higher BMD in spine and 1–2% in hip. Combination therapy when compared to single therapy showed continued suppression of the biochemical markers of bone resorption. Enough data are lacking on further fracture reduction.

Diagnosis of Osteoporosis

BMD defines the diagnosis of osteoporosis. It is reported as T-Score measured by DXA based on reference data obtained by DXA according to WHO. This WHO diagnostic criteria can be applied to women in transition phase of menopause. Indications for BMD measurement in women during the transition of menopause are for those having clinical risk factors for fracture, such as low body weight, prior fracture or high-risk medications [42].

Indications for DXA (Grade B) given in Table 2.

Definition of Osteoporotic Fracture Risk

BMD defines fracture risk (both primary and secondary causes) which is classified as low-, moderate- and very high-risk.

Management Plan as given in Table 3.

How Long to Treat

BMD testing every 1 year after starting therapy and every 2 years after that.

Current Indications for Hormone Therapy

There are 3 indications for postmenopausal HT, which have been time-tested and these are symptom relief, urogenital atrophy, and bone [7]. Early menopause: within 10

years of menopause. Late menopause: beyond 10 years of menopause.

Indications in Bone Health

1. EPT/ET is a cost-effective treatment in the early period of menopause, especially in women with symptoms of osteoporosis, unless contraindicated. HT prevents the osteoporotic fractures, also in low-risk populations [46, 47].

2. All preparations of estrogen, including low-dose and non-oral routes, are adequate for bone health. Transdermal route should be the preferred in women at high risk for deep vein thrombosis (DVT), stroke, and CVD [48].

3. Stoppage of HT leads to loss of bone protective effect. Women with reduced bone mass after 10 years of menopause can opt for extended use of HT after detailed counselling of the risk and benefit and also comparing the other available options. [49, 50].

4. For prevention of bone loss in women with premature menopause and secondary amenorrhea HT should be given as primary therapy.

5. Primary HT workups, counselling and compliance for annual follow-ups are mandatory before prescribing HT.

Contraindications of Hormone Therapy are given in Table 4.

Hormone Therapy in Women with Uterus

Addition of progestins to estrogen reduces the risk of endometrial hyperplasia and malignancy, which can occur with unopposed estrogen. For women who underwent endometrial ablation, progestogen must be given as some endometrial tissue can be present in uterus, even with prolonged amenorrea. Progestins, with androgenic properties can be preferred to protect the hip.

Hormone Therapy in Hysterectomized Women

Only estrogen is given to women without uterus and there is no need for a progestogen. Those who had history of endometriosis may need estrogen–progestin therapy.

Risk–Benefit Analysis

There is slight increase in the risk of invasive breast cancer with EPT; the absolute increase being less than 0.1% per year. WHI has shown reduction in the risk of breast cancer with ET.

The risk of venous thromboembolism (VTE) is 2 per 1000 per year in women aged 50–60 years. Risk is maximum in the first year of treatment which increases with advancing age, obesity, and previous history of VTE. HT should be discontinued temporarily during surgery or any immobilization, including travel.

The risk of stroke is increased with ET and EPT (hazard ratio is 1.39) in the WHI study, similar to the Nurses Health Study; which is contrary to the Danish Nurses Study. In this study, unopposed 1 mg estradiol per day was given to 13,122 healthy postmenopausal women who were followed for 5 years and had a protective hazard ratio of 0.80; this indicates that outcome is influenced by the type and dose of estrogen and also the chosen population.

HT when started within 10 years of menopause may benefit cognition and Alzheimer's disease but when started beyond age 65 it can worsen cognitive function and found to have no benefit on Alzheimer's disease.

WHI and Nurses Health Studies had shown a cardioprotective effect when HT was started close to menopause with a relative risk of 0.66.

There is 2–5-fold increased risk of endometrial cancer in women using estrogen without adding progesterone.

EPT reduces the risk of colorectal cancer.

Hormone Therapy Regimens

Several types of regimens are available while prescribing ET. Clinical goal is to maintain benefits of estrogen with protection of uterine endometrium and reducing unscheduled uterine bleeding, which affects compliance.

Several types of regimens are: cyclic, cyclic-combined, continuous-cyclic, continuous long-cycle, continuous-combined, and intermittent combine (Table 1).

Perimenopausal Woman

Monthly or trimonthly cyclic regimens are options for this population. Women having infrequent menstruation and progestogenic side effects should be given a trimonthly preparation. As there is high risk of irregular bleeding, so continuous combined regimens should not be used in perimenopausal women [51].

Table 1 Regimes of hormone therapy

Regimen	Estrogen	Progestogen
Cyclic	Days 1–25	Last 10–14 days of the cycle
Cyclic-combined	Days 1–25	Days 1–25
Continuous-cyclic (sequential)	Daily	10–14 days every month
Continuous long-cycle	Daily	14 days every 3–6 months
Continuous-combined	Daily	Daily

Postmenopausal Woman

Continuous combined treatment may reduce risk of endometrial cancer when compared to sequential regimens. Continuous combined regimens induce endometrial atrophy (see Table 2).

Women can present with irregular bleeding or spotting during the first 4–6 months of continuous combined therapy, so it does not warrant investigation. Endometrial assessment must be considered if the bleeding becomes heavier rather than lighter, persists beyond 6 months, or occurs after a significant time of amenorrhea. The incidence of irregular bleeding may be reduced by increasing the ratio of the progestogen to the estrogen [51] (see Table 3).

A systematic review assessing changes in BMD over a 2 year trials in the past decade showed no obvious difference between the various estrogen compounds (oral, non-oral, human, and non-human estrogen) [51] (see Table 4).

Table 2 Indications for DXA

Indications for DXA (Grade B)	More than 5 years since menopause
	Less than 5 years of menopause with risk factors
	Women in menopause transition with secondary causes
	Osteopenia evidenced by radiology and presence of vertebral compression fracture
	Fragility fractures seen in women on radiology or DXA
	Emerging indications are to measure total body fat and lean tissue mass
This suggestion is based on the following:	Natural menopause seen at early age in Indian women, which is 46.5 years [43]
	The life expectancy of an Indian woman being 70.3 years
	Accrual of low peak bone mass [44]
	Clinical presentation of fracture at an early age
	Accelerated bone loss within 5 years of menopause [44]
	More than 40% of women beyond age 40 years have low bone mass which increases to more than 80% after 65 years
	Screening can reduce the hip fracture risk by 20% as shown by a meta-analysis of the three trials [45]

Table 3 Management plan

Management plan includes	Categorizing risk by clinical factors alone or by BMD
	Confirmation of diagnosis by DXA
	Excluding secondary causes—Complete Blood picture, serum 25 hydroxy vitamin D, serum calcium and serum alkaline phosphatase
	Counselling all about lifestyle changes
	Giving appropriate pharmacotherapy and follow-up
Therapeutic Lifestyle management	For low bone mass and lower risk of fracture: reassurance, enforce lifestyle measures
	Nutrition: an adequate ingestion of calcium (1–1.5 g/day), Vitamin D (> 1000–2000 IU/day), Vitamin K (1 mg/day), and magnesium
	Habits: avoid alcohol and tobacco
	Exercise: weight-bearing, strength training and balance exercise tailored to the need under supervision
	Fall Prevention: 30% of persons 65 years and older fall, 50% of persons over 80 years and older fall, 5% of them will have a fracture, and 1% will have a hip fracture
Whom and when to treat	Treatment is decided by the severity of the fracture risk, the cost of intervention, risk benefit analysis, the active participation of the patient and the correct guidance by the physician
	Low bone mass with more than two risk factors have high risk of fractures and osteoporosis without fracture are candidates for HT
	Premenopausal: hormone therapy, others if estrogen therapy is contraindicated
	Perimenopausal: hormone therapy, bisphosphonates
	Postmenopausal:
	Less than 10 years: hormone therapy, raloxifene, tibolone, bisphosphonates, calcitonin, denosumab, parathyroid hormone
	More than 10 years: bisphosphonates, calcitonin, denosumab, parathyroid hormone

Table 4 Contraindications of hormone therapy

Contraindications of Hormone Therapy	Active endometrial and female hormone-dependent cancers
	Active breast cancer and any estrogen/progesterone receptor-positive cancers
	Pregnancy
	Vaginal bleeding under evaluation
	Impaired liver function result or any active disease in liver
	History of venous thrombosis provoked by estrogen inherent risk of thromboembolism
Relative contraindications	Migraine
	Thrombophlebitis in superficial veins
	Family history of breast cancer in first degree relative
	Leiomyoma
	Endometriosis
	Disease of gall bladder

Duration of Therapy

ET and EPT are recommended for different duration of treatment. ET has a better safety profile, so it can be given for a longer time in the absence of adverse effects and other risk factors. For ET, more benefit was observed during a mean of 7 years of use and 4 years of follow-up. For EPT, duration is limited by the increased risk of breast cancer and breast cancer mortality associated with 3–5 years of use (see Table 5).

Essential Factors to Lower the Risks and Side Effects of HT

- Age of initiation: ideally, HT should begin within 10 years of menopause or by 60 years of age.
- Low dose regimen should be used as appropriate.
- Route of administration: transdermal route has a less risk of thrombosis compared with oral administration which has a high risk for DVT, CVD, or stroke.
- Type of progestin: side-effect profile varies with different progestogens. The newer progestin drospirenone (a

derivative of spironolactone) should be considered in hypertensive women; natural progesterone is also a good choice. Ethindrone derivatives do not have a preferential bone protective effect.

Individualized benefit–risk profile should be constructed for every woman planning any HT regimen. It depends on women's situation, severity of symptoms and their effect on her quality of life. The absolute risks are low for the use of HT in healthy women ages 50–59 years. Whereas, long-term standard dose HT, or HT initiation in older age is associated with greater risks.

HT workup and follow-up please see Table 5.

Follow-up

Initially, 3 months and later yearly check-ups.

Table 5 Work-up and follow-up for hormone therapy

Clinical History and Examination	Evaluation of woman's needs, risk profile
	Risk assessment for Diabetes Mellitus, CVD, Alzheimer's disease, DVT, Osteoporosis and cancers
	Family history of fractures, CVD and breast cancer
	Physical examination: BMI, pulse, blood pressure, breast examination, abdominal and pelvic examination
Investigations	Complete Blood Count
	Urine Routine analysis
	Fasting blood glucose level
	Lipid profile
	Pap smear/cervical cytology
	Transvaginal sonography of uterus and adnexa

Conclusion

Today, we have strong evidence for role of MHT as a first line therapy in early postmenopausal women for a low risk for fractures, low bone mass and management of osteoporosis without fragility fractures. Estrogen replacement therapy, if recommended by an orthopedician, should be prescribed with the joint consultation of a gynecologist or an endocrinologist.

Declarations

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Standard Statement This article does not contain any studies with human or animal subjects performed by the any of the authors.

Informed Consent For this type of study, informed consent is not required.

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