

Menopausal Osteoporosis: A growing challenge

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Menopause is defined as a normal biologic event marked by permanent cessation of menstruation resulting from loss of ovarian follicular activity. Natural menopause can only be established in retrospect, after 12 consecutive months of amenorrhoea.

Menopause occurs at a median age of 51 years (1-3). The age of menopause appears to be determined genetically and does not seem to be related to race or nutritional status. Menopause occurs earlier in cigarette smokers (3), in some women who have had hysterectomies (4) and in nulliparous women.

The problem of menopause has assumed a great importance during the course of this century because there has been a striking increase in overall female life expectancy. Thus many women are now living beyond the time of menopause and into old age. More than 30% of the female population of the United States is postmenopausal and this percentage is increasing (5).

Following menopause, is a period of relative ovarian quiescence leading to decreased cyclic hormone production. Hormonal changes, in turn, cause many symptoms like amenorrhoea or abnormal bleeding, hot flushes, sleep disturbances, changes in mood and behaviour, loss of libido, vaginal and urinary tract changes.

However, two major long term consequences,

osteoporosis and arterial disease require special attention as they account for major morbidity and mortality.

OSTEOPOROSIS is defined as a systemic skeletal disease characterised by low bone mass and micro-architectural deterioration of the skeleton, leading to enhanced bone fragility and increased fracture risk (6).

Osteoporosis is now recognized as one of the most serious problems. It is estimated that about 30% of postmenopausal women are osteoporotic (7). It is an underlying condition, like hypertension or hypercholesterolaemia, that often remains symptomless or 'silent' until the medical complication occurs, which in this case is an osteoporotic fracture (8). The number of elderly women who have osteoporosis related crush fractures of spinal vertebrae or fractures of either the radius or the neck of the femur have reached epidemic proportions (9).

In India, it is assumed that approximately 35% of postmenopausal women develop osteoporosis and coupled with the increasing number of postmenopausal women, the problem would soon assume large proportions (10), while in US, osteoporosis affects more than 25 million people, 80% of which are women and it accounts for more than 1.3 million fractures annually

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including more than 500,000 of the spine, 250,000 of the hip and 240,000 of the wrist (8). Hence currently, on an average a woman has 15% chance of experiencing a hip fracture in her lifetime (11). Five to twenty percent of hip fracture victims will die within 1 year of the fracture event from medical complications and more than 50% of the survivors will be incapacitated, many of them permanently (12).

Thus the devastating consequences of osteoporosis including fractures have led to increased morbidity, mortality and big financial burden, making it as a major public health problem.

Etiology and Risk Factors

The cause of osteoporosis is multifactorial. The primary factors associated with osteoporosis include age, heredity and estrogen status.

Age is the most important factor associated with bone loss (13). Peak bone mass is attained between the ages of 25 and 35. Bone mass then begins to decline. Before menopause, the rate of loss is less than 1% of total bone tissue per year. However, the period of accelerated bone loss usually follows menopause, averaging 2% per year for the next 5 to 10 years. This period is followed by a slower rate of bone loss resulting in lifetime losses of about 35% of cortical bone and 50% of trabecular bone mass (8). Lifetime losses may reach 30 to 40% of peak bone mass in women (12). This leads to an increased risk of fractures specially those of hip, wrist and vertebrae. Evidence suggests that this may be related to the gradual decrease in growth hormone levels associated with age (14).

Heredity plays a role primarily by determining the peak bone mass that a woman will attain during her life and the subsequent rate of bone loss. Thus

postmenopausally, a woman may experience a fast rate of bone loss but may not suffer fracture because of a high adult peak bone mass. Conversely, a woman with a slow rate of postmenopausal bone loss may suffer fracture because her adult peak bone mass was low. On an average, African-American women have a much higher bone mass than white women, and this may explain the low risk of osteoporotic bone fractures observed in African-Americans (15). A family history of osteoporosis is a strong risk factor. It has been well observed that there is reduced bone mineral density (BMD) in daughters of osteoporotic women and reduced BMD in men and women with first degree relatives who have osteoporosis (16,17).

Another factor associated with bone loss is estrogen status. For women not taking estrogen replacement, bone loss after menopause is accelerated to a rate of 3-5% per year (18). This loss is most rapid during the first 5 years after menopause, when up to 20% of the expected lifetime loss from the femoral neck may occur (19).

Other risk factors which can cause osteoporosis are prolonged periods of amenorrhoea during the reproductive era, heavy tobacco, caffeine and alcohol consumption, sedentary life style, high protein diet, inadequate calcium and vitamin D intake, underweight women or women with small build, late menarche and anorexia.

Pathogenesis

Osteoporosis is a disorder in which bone resorption exceeds formation. The imbalance is because of altered remodelling process due to decreased number of osteoblasts or functional capacity of osteoblasts. Each remodelling sequence in osteoporosis results in a definite

bone deficit at the end and if this process continues, there will be increased rate of bone loss (7). The fall in estrogen levels during postmenopausal period is associated with increased production of cytokines, resulting in increased number and activity of osteoclasts in the remodelling (20).

Manifestations

Osteoporosis, as such, is silent. Its clinical importance is that it may lead to fracture which produces pain and deformity. Most common fractures to occur are forearm fracture (colle's), hip fracture and the vertebral fractures. Hip fractures are the most severe and are associated with significant morbidity and mortality. Significant collapse of one vertebral body usually leads to severe pain. In addition to repeated pain, numerous crush fractures result in loss of height and often a marked kyphosis ('dowager's' or 'widow's hump'). Because movement of thoracic cage becomes limited, cardiopulmonary embarrassment may ensue leading to severely reduced exercise tolerance and disability (7,21,22).

Diagnosis

Diagnosis of osteoporosis used to be made with the occurrence of fracture in the past. However, it is desirable to identify those who have the condition before complication occurs. This can be achieved by measuring bone mass (or density) by different available tools which have an accuracy exceeding 95% and a precision error less than 1% (12). X-rays are relatively insensitive as they depict bone loss only when there is loss of 30-50% of bone mass, however, they may help in patients requiring aggressive intervention (20).

As yet, there is no accurate way to measure bone quality but bone densitometry tests are now available to measure bone quantity (23). Various densitometry

techniques for quantitative measurement of bone mineral density are :

- Dual-energy x-ray absorptiometry (DEXA)
- Quantitative computed tomography
- Quantitative ultrasound
- Radiographic absorptiometry
- Single-energy x-ray absorptiometry

DEXA, is considered a 'Gold Standard' in diagnosis of osteoporosis because of low radiation exposure, high precision and accuracy, ability to scan the entire skeleton, short scanning time, higher resolution and sensitivity.

Recently the ability of quantitative magnetic resonance (QMR) and high resolution MR Imaging (MRI) to assess osteoporosis is being explored.

The results of the densitometers are interpreted in terms of T-Scores and Z-Scores. T-Score describes the bone mass of the patient compared to the mean peak bone mass of the normal young adult reference population using standard deviations (8), while the Z-Score compares the patient's bone mineral density (BMD) with the mean BMD for a person of the same age (20). The World Health Organisation defines osteoporosis using T-Score as follows (7) :

Definition of osteoporosis based on T-Scores

Normal	A value of BMD within 1.0 SD of the young adult reference mean.
Osteopenia	A value of BMD that is more than 1.0 SD below the young adult mean but less than 2.5 SD below this value.
Osteoporosis	A value of BMD that is 2.5 SD or more below the young adult mean.
Severe Osteoporosis	A value of BMD that is more than 2.5 SD below the young adult mean in the presence of one or more fragility fractures.

BMD = Bone mineral density SD = Standard deviation.

All postmenopausal women who have not been previously screened by the age 65 should undergo densitometry. Of special concern are women with height loss or evidence of osteoporotic fracture (24). In perimenopausal women, BMD should be measured whenever the information needed to make an informed decision regarding HRT or when any risk factor for osteoporosis is present. (25-27).

Biochemical Markers

Bone loss can be measured by repeated bone density determinations, but this does not provide immediate feedback to the doctor or patient and can be expensive as well as inconvenient. In osteoporosis, the bone turnover is increased resulting in an increase in markers of bone formation and bone resorption.

Biochemical assays for monitoring turnover all rely on the measurement in the serum and urine, of enzymes or matrix proteins synthesized by the osteoblasts or osteoclasts that spill over into the body fluids or of the osteoclast-generated degradation products of the bone matrix itself (28).

Biochemical markers of bone turnover allow clinicians to evaluate the risk of bone loss and provide insight into response to therapy. Markers may be particularly useful for monitoring therapeutic responses and encouraging patient compliance, as well as in settings where bone mass determinations are not available. As technology improves, tests for these markers will become more reliable and more widely available. In fact, home monitoring of cross-link excretion is already being studied; the procedure would be similar to a home pregnancy test.

Biochemical markers of bone formation are :

- Serum total and bone alkaline phosphatase
- Serum osteocalcin
- Procollagen I extension peptides

Biochemical markers of bone resorption are :

- Fasting urinary calcium, hydroxyproline and hydroxylysine glycosides
- Plasma tartrate-resistant acid phosphatase
- Collagen pyridinium crosslinks and type I collagen telopeptide breakdown products

Management of Osteoporosis

As recently as a decade ago, osteoporosis was regarded as an inevitable part of aging, we expected women to "get littler as they got older" and eventually break a wrist or rib. But now there are tools to spot at risk patients before fracture occurs and drugs to reduce or even reverse risk. The primary goals of treatment for osteoporosis include (8) :

- Increasing bone mass.
- Stopping or reversing bone loss by inhibiting bone resorption and/or stimulating bone formation.
- Reducing the incidence of osteoporotic fractures.

Prevention and treatment of osteoporosis can be achieved by methods including lifestyle modifications like avoiding tobacco, cigarettes, excess of alcohol and coffee, doing weight bearing exercises at least 3-5 days per week, preventing falls as well as ensuring an adequate exposure to sun and taking a diet rich in calcium and vitamin D (29,30).

Various drugs used in the treatment and prevention of osteoporosis are (31) :

(a) Antiresorptive agents

Estrogen, Progestogen,
Bisphosphonates, Calcium, Calcitonin.

(b) Bone formation agents

Fluoride, Parathyroid Hormone

(c) Agents with unknown action

Vitamin D & analogues, Anabolic steroids, Ipriflavone

Hormone Replacement Therapy

The term hormone replacement therapy or HRT means use of estrogens, either alone or in combination with progestogen. During last few years considerable evidence has accumulated that HRT reduces the risk of long term sequelae of menopause like osteoporosis. HRT can fulfil both preventive and therapeutic roles. The mechanism by which estrogen produces its effects on skeletal remodelling is not completely understood. Estrogens decrease the rate of bone resorption principally by an inhibition of osteoclastic activity. Estrogen replacement therapy helps maintain bone mass and skeletal integrity thereby protecting against osteoporosis (32), oestrogen conserves calcium by both enhancing the efficiency of intestinal absorption and by improving renal calcium conservation (33). In addition, oestrogen appears to have a direct effect on osteoblast function (34). Although oestrogen can effectively slow bone loss, it can conserve, to a limited degree, the bone loss associated with osteoporosis (35). For this reason oestrogen replacement therapy should be initiated at menopause and should be given for a long term, although optimal duration is unclear. Estrogens have been demonstrated to reduce bone remodelling and prevent bone loss when given by any route of administration. Thus, oral, transdermal, percutaneous, subcutaneous and vaginally administered estrogen are all effective if given in adequate doses.

Progestogens are used along with estrogen in women with intact uterus to reduce the risk of endometrial hyperplasia. Evidence has suggested that progesterone also has a role in maintaining bone density (36), progesterone appears to promote bone formation by increasing osteoblast activity either directly or indirectly, by inhibiting the glucocorticoid effect on osteoblasts. This finding supports the use of a progestin

alone in women who are unable to take oestrogen therapy.

Tibolone (Livial), a gonadomimetic preparation has a weak oestrogenic, androgenic and progestogenic activity. Besides the prevention of osteoporosis, it improves the mood and libido and does not cause endometrial proliferation.

Reduction in fracture rate has been well documented at all sides with HRT. In addition, this also improves other associated menopausal symptoms (37).

Short-term adverse effects of hormone replacement therapy include vaginal bleeding, breast tenderness and upper GI symptoms (31). But the major problem and threat with estrogen therapy is breast and endometrial carcinoma. Secondly the compliance with HRT is poor and discontinuation rate is very high (8).

The present strategies for the use of hormone replacement therapy for osteoporosis must therefore, take into account the likelihood that long term, probably life-long, therapy after menopause is required optimally to protect against fracture ; against this background the important but only partially characterised extraskeletal risks and benefits must also be considered.

Bisphosphonates

Bisphosphonates are analogues of pyrophosphates. There are three generations of bisphosphonates and antiresorptive properties increase approximately ten-fold between generations. First generation bisphosphonates are—etidronate and clodronate, second generation compounds are—alendronate, pamidronate and tiludronate, third generation—risedronate.

Bisphosphonates inhibit bone resorption (38). They shorten the life span of osteoclasts, interfere with

resorptive action of mature osteoclast, reduce activation frequency, stimulate osteoblasts to produce substances that inhibit osteoclast and decrease levels of osteoclasts stimulators-interleukin-6.

Etidronate is not approved in United States for the treatment of osteoporosis. However, it is approved in 22 other countries. Alendronate is approved by US-FDA for prevention and treatment of postmenopausal osteoporosis. It has been seen to reduce vertebral fracture rate by 50% (39). The propensity of etidronate to inhibit bone mineralisation necessitate its cyclic use. However, alendronate does not inhibit bone mineralisation and is considered in a continuous oral daily dose of 10 mg.

Calcium

Calcium intake decreases significantly after childhood. Beneficial effects of calcium supplementation on bone mass have been well documented in children and adults (31). Dietary calcium, primarily in the form of dairy products, has been shown to be associated with decreased bone loss in premenopausal women but does not increase bone mass (40,41). Among supplement, calcium citrate is best absorbed, but calcium carbonate is less expensive and is absorbed well if taken with meals. At present, there is no definite evidence that calcium therapy alone reduces fracture risk. However, beneficial effects have been seen with calcium supplementation as an adjunct therapy to other treatments especially in patients with low calcium diet. The recommended dose for calcium in postmenopausal women, without estrogen treatment, is 1500 mg./day and 1000 mg./day for those taking estrogen therapy (42).

Vitamin D and its Analogues

Vitamin D deficiency is common in elderly,

particularly in those persons who are no longer fully independent and therefore, less exposed to sunlight. By treating vitamin D deficiency, secondary hyperparathyroidism and the resulting increase in bone loss will be eliminated. Beneficial effects on bone mass in postmenopausal osteoporosis have been reported with the active metabolites of vitamin D, calcitrol and its analogue, alfacalcidol. Calcitrol can increase lumbar bone mass and decrease the rate of vertebral fracture (43). Reduction in bone loss and risk of fracture has been well documented with supplementation of 400-800 IU of vitamin D per day. Vitamin D status can also be normalised in elderly, by facilitating time outdoors, with 15-30 minutes daily being adequate in temperate climate.

Calcitonin

Calcitonin, is secreted by thyroidal C cells and is rapidly degraded after oral administration by high concentrations of peptidase in gastric secretions. Calcitonin causes the brush borders of osteoclasts to disappear and thus osteoclasts move away from bone resorption surface. This inhibits osteoclast function, reduces lifespan and number of osteoclast. Calcitonin also has analgesic action through stimulation of endorphins and thus can reduce pain in osteoporotic fracture also. Calcitonins available for use are porcine, human (synthetic), salmon (synthetic) and eel. Salmon calcitonin is the most potent (8). Both injectable since 1984 and nasal spray since 1995 are being used in treatment of postmenopausal osteoporosis. In India, only injectable form is available and its administration can lead to side effects like rash, flushing, dizziness, nausea and thus compliance becomes very poor. Calcitonin is considerably more expensive than HRT or the bisphosphonates and less effective than estrogen (7,44)

and is probably best reserved for the treatment of osteoporosis in which HRT or bisphosphonates are contraindicated or ineffective.

Fluoride

Fluoride is a known agent that can stimulate bone formation and substantially increase bone density (45). However, its role remains unclear because of potential toxicity and inconsistent results concerning anti-fracture effectiveness.

Preliminary data on **parathyroid hormone** looks promising, but current formulation must be injected and injectable agent would have to demonstrate sustained superiority to be accepted by the patients.

Safety profile and anti-fracture effect of **anabolic steroids** and **ipriflavone** is not well established yet.

Osteoporosis—Future

The social, human and economic burden of osteoporosis is huge on the society. In US, cost of a hip fracture alone may exceed \$ 240 billion within 50 years (46). This major health problem thus needs priority not only in implementation of available modalities of therapy at the earliest but also in discovering newer and advanced therapies for prevention and reversion of osteoporosis.

The improvement of therapeutic regimens will depend on the extent of investment of the pharmaceutical industry, which, in turn, depends on the recognition of the disease as a major health problem by authorities. Nevertheless, who will benefit from a particular therapy, the cost benefit ratio of treatments, duration of treatment are the future challenges. However, we expect that within the next decade some of the currently used treatments will disappear, some of them will be significantly improved and some new ones will be developed.

Hormone replacement therapy is the first line therapy and reduces fracture risk between 30% and 50% (47) but remains a clinical challenge, as many patients stop treatment within the first few months. Better combined HRT preparations need to be developed in order to reduce side effects and therefore, improve compliance. In addition to the oral, transdermal and percutaneous routes, a new nasal spray route of administration has been developed and thus broader range of formulations and routes of administration may help in improving compliance.

In recent years, number of new compounds have been developed in an attempt to retain the beneficial skeletal and cardiovascular actions of estrogen without adverse effects on the endometrium and breast. Estrogen analogues—Selective estrogen receptor modulators (SEMRs) Tamoxifene, droloxifene, raloxifene, will have therapeutic potential for prevention and treatment of osteoporosis.

Bisphosphonates represent the first alternative to HRT as they reduce risk of fracture by 30% (48) but new formulations should be developed to increase intestinal absorption and to reduce oesophageal irritation. A patch formulation is already under development and may overcome some of these problems (transdermal delivery of Zolendronate is now in phase II clinical trials). New bisphosphonate with greater potency are also on a way (ibandronate, olpadronate and incandronate). However, more research is needed regarding optimal doses and regimens, (continuous versus intermittent, oral versus parenteral) comparisons with other agents and their use in combination with other agents.

Calcitonin is still an interesting antiresorptive therapy, given its excellent safety profile. The development of analogue with increased potency, that could be reliably administered by the nasal or even oral route would be a

significant advance. Vitamin D metabolite with anabolic effect on the osteoblast without stimulating osteoclast and with moderate effect on intestinal absorption of calcium would certainly be welcome.

Stimulators of bone formation like fluoride analogues, analogues of PTH and several growth factors (TGF β and IGF 1 and 2) may have a significant role in treatment of osteoporosis till their safety profile is clearly established.

However, the ideal treatment of osteoporosis would be an uncoupling agent that would decrease bone resorption and stimulate bone formation concomitantly, without impairing bone quality. Such an agent does not exist today but may not be unrealistic with increasing knowledge.

Finally, to achieve the goal of reducing the burden of osteoporosis, the public, medical profession and politicians have to be made aware of the size of the problem for the individual and society.

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