Osteoporosis — Incidence and Implications

Usha Krishna, Rajeev U. Mehta
Clinic For Women, Ajit Villa, Laburnum Road, Gamdevi, Mumbai 400 007.
Sterling Osteoporosis Detection Centre, L.D. Ruparel Medical Centre, Dr. Annie Besant Road, Worli, Mumbai 400 025.

Usha Krishna

The proportion of elderly population is rapidly increasing in the developed and the developing world. The aging population and public health workers are concerned about the disability, dependence and associated economic and social problems that are caused by osteoporosis and cardiovascular disease.

Osteoporosis is the result of deterioration of the microarchitecture of bone tissue signified by reduction in bone mass and consequential increase of bone fragility and increase of risk of fractures. Hormone Replacement Therapy (HRT) is the most accepted treatment for prophylaxis as well as management of osteoporosis. The treatment can be started in the perimenopausal period for climacteric and urogenital problems but its continuation for long term for at least 5 to 10 years, is necessary to achieve optimal benefit in decreasing the possibilities of osteoporosis and cardiovascular disease. Proper counselling and individualization of treatment is necessary as HRT may not be suitable or required for every woman and alternate treatment can also be considered.

Material and Methods

656 menopausal women were studied over the last nine years in the "Clinic For Women". The first study of 450 women was focused on urogenital and climacteric problems. Thereafter 206 recent cases underwent bone mineral density (BMD) measurement. The present study was carried out to assess the extent of osteoporosis in these women and the compliance as well as effectiveness of treatment. A detailed history specially related to menopausal problems and general medical problems was noted. High risk factors such as surgical menopause with oopherectomy, premature ovarian failure, thyroid replacement therapy or history of treatment with glucocorticoid etc. were noted. 71 of these 206 women had surgical menopause. 44 women had vaginal or abdominal hysterectomy and 27 had bilateral salphingooopherectomy along with hysterectomy. There were 10 cases of premature ovarian failure, 15 cases had been on thyroid replacement for hypothyroidism and two women had long term glucocorticoid therapy.

A general physical examination including height, weight and blood pressure, breast examination and gynaecological examination along with Pap smear for cytological abnormalities and maturation index was carried out. Appropriate laboratory tests were carried out. Complete blood cell counts, blood sugar, lipid profile and coagulation factors, gonadotrophin estimation and tests for thyroid and parathyroid hormone concentration were studied in appropriate cases. Blood and urine tests to assess the extent of bone demineralization were carried out in 20 patients. The incidence of osteoporosis and its relation to age, years of menopause, associated risk factors, and co-relation with other menopausal symptoms were noted. The bone mineral density was measured by dual energy X-ray absorptiometry (DXA). Fifty four patients also had bone density study by ultrasonography. Transvaginal sonography for uterus and adenexe was done and the thickness of the endometrium was noted. This was repeated at 6 to 12 months, especially if the patient had post menopausal bleeding during the therapy.

Endometrial biopsy was necessary in only one case who had bleeding on and off although the endometrium was just 2mm. in thickness. Mammography was recommended to all. 140 of the 206 women underwent mammography.

Of the 206 women, 108 were on HRT; 60 were put on Tibolone (Livial), 20 on Estriol (Evalon), 18 on (Progynova), 5 were on conjugated estrogen (Premarin), 3 received skin patches and 2 were on Gel. All the women with intact uterus had progestogen as part of HRT. 20 patients have been on HRT for 11 months or more and they had repeat bone density study to note the effectiveness of HRT. 11 patients received alendronate, 2 patients raloxifene and 2 cases with severe osteoporosis had both HRT and alendronate.

Results

The commonest presenting symptoms were urogenital problems (85%). These are related to the years of menopause and are associated with atrophic changes and loss of collagen from connective tissue. 25% of the women had musculo-skeletal problems such as backache. Climacteric symptoms, depression, insomnia and irritability was noted in 22%. Vaginal cytology indicated that 85% of women had atrophic smears and about half of them had atrophic inflammatory smears. A large number of women came for check-up and Pap smear during their menopausal period and 25 of these 206 patients specifically asked about HRT. The average age of menopause in this study was 48.3 years. Of 206 cases who underwent bone density study 100 (48%) had osteoporosis, 79 (38.4%) had osteopenia and 27 (13.1%) were normal. Table I shows the relationship of osteoporosis with age and Table II shows the relationship of osteoporosis with the number of years of menopause. There is a definite co-relation of incidence of osteoporosis with age and even greater co-relation with the number of years of menopause. 80 percent of women with osteoporosis had uro-genital problems and 30 percent had past or present complaint of climacteric problems. Though it requires long term treatment with HRT to show improvement in bone density, the present study of 20 cases followed up for 11 months indicates some improvement in bone density in 60% of them. All patients except 8 felt an improvement in general well being and musculoskeletal as well as climacteric and urogenital symptoms. 20 women required vaginal estrogen creams for senile vaginitis.

It is worth noting that in our first study which was carried out five years ago, the compliance rate was poor. Only 12% of the 450 women continued HRT for more than one year and 5% for more than five years. Women have greater awareness of menopausal problems today and are keen to continue the treatment and have better quality of life. Of the next group of 206 women three fourths of them came for follow-up visits and are on regular HRT or the treatment that has been advised. The incidence of diabetes in this group is 11%, hypertension 17% and ischaemic heart disease 3%. These women were appropriately referred and treated but about half of them had great hesitation in going to one more clinician for further treatment.

Discussion

The worldwide incidence of osteoporosis is rising because of increase in the aging population and sedentary lifestyle. About one in three post-menopausal women in USA are affected by osteoporosis. Approximately 60 million people at present have osteoporosis in India. As the life expectancy is increasing even in the developing countries, by the year 2035, the maximum number of osteoporosis cases in the world will be in India and China. A woman when not treated, looses 50% of the bone mass by the time she is 70 years old whereas a man looses 25% of his bone mass when he is 90 years. For women, this increases the risk of fractures and disabilities.

Long term HRT has been reported to reduce the risk of osteoporotic fractures by 50%. The National Osteoporotic Foundation (NOF) recommends that women who take HRT for long term do not need BMD measurement until age 65. Delaying the use of HRT greatly reduces its benefits and therefore timely start and compliance are essential factors in prevention of osteoporosis.

Pathogenesis

With declining ovarian function and dimunition of estrogen levels, the female skeleton undergoes increased

bone remodeling and the rate of bone loss increases from the perimenopausal period. The normal bone building takes place till about 30 years of age and after that, as the part of natural aging process, the break-down of bone is faster than the formation. Women who are deficient in nutrition and calcium intake, start with lower peak bone mass and are therefore are at a greater disadvantage. Immobilization, inactivity and poor muscle strength increase the bone loss considerably. The bone mass declines after menopause, but women who are hypo-estrogenic such as those with premature ovarian failure have earlier onset of menopause. The secondary causes of osteoporosis are related to drug use such as corticosteroids, anticonvulsants, heparin and phenothiazines. Hyperthyrodism and estrogen deficiency due to early oopherectomy, eating disorders, pituitary tumor, multiple myeloma, chemotherapy, hyperparathyroidism are other important factors. High dose or long term glucocorticoid treatment for diseases such as rheumatoid arthritis, asthma, Crohn's disease, ulcerative colitis, multiple sclerosis, sarcoidosis or in organ transplant patients, increase the risk of osteoporosis. The trabecular bone with its high surface area, appears to be particularly prone to the adverse effects of glucocorticoid therapy with uniform thinning of the trabeculae. Smokers and those on excessive alcohol intake are more prone to develop osteoporosis. Genetic factors such as osteogenous imperfecta and hemoglobinopathies are also important. There is a genetic predisposition to osteoporosis and therefore a family history is important. Besides, the problem is more prevalent in white Caucasian women and next are the Asian women and then the black races. The bone mass starts declining at around 40 years and the rate of loss varies between 0.25 to 1% per year; the loss being higher in trabecular bone (1% to 5%) than the cortical bone. The increased bone resorption due to decrease in estrogen hormones, fall of serum calcium and Vitamin D3 as well as parathyroid hyperplasia diminishes bone mineralisation. The osteoclastic activity is far more than that of osteoblasts. Besides, decrease in muscle strength and diminished sense of balance leads to falls and fractures. Type I Osteoporosis influences the trabecular bone, the vertebra, distal forearms and mandible. Type II affect the cortical bone such as hip bone, proximal humerus, tibia and pelvis. Decrease in serum estrogen and increase in inter-lukein 1 and 6, increased osteoclast activity and tumor necrosis factors along with decrease in replicate activity of osteoprogenitor cells and synthetic activity of osteoblasts as well as biological activity of matrix bound growth factors lead to Type II osteoporosis. The strategies for prevention and treatment of osteoporosis are aimed at minimising bone loss, and preserving or increasing bone mass and decreasing the risk of falls.

Clinical Presentation & Diagnosis

Osteoporosis does not have a dramatic clinical presentation except when presented with fractures. It is therefore, called a 'silent epidemic'. Chronic backache, loss of height and kyphosis are features of crush vertebral fractures but hip fractures and Colles' fractures present as emergencies. When the fracture occurs without significant trauma in an elderly woman, it should be suspected to be a result of osteoporosis.

BMD measurement

BMD measurement is specially indicated in the high risk cases or when it is necessary to make a decision regarding treatment. For prophylactic treatment, the BMD study is not necessary. It is the single best diagnostic tool which can determine the fracture risk and identify patients who need intervention. For every decrease in bone mass of one standard deviation, the relative risk of fracture increases 1.5 to 3.0 fold. The bone mineral density is expressed in gm/cm.sq. The BMD measurement is carried out at both lumbar spine (L1 to L4) and hip (femoral neck. trochenteric region, Ward's triangle and total hip) using QDR 1000 plus DXA bone densitometer. To ensure correct and uniform analysis of all patients, a quality control procedure like scanning of Anthropomorphic spine phantom is routinely undertaken throughout the study period to demonstrate the stability of calibration of the DXA Bone densitometer. The DXA studies are expressed in T & Z scores. T-score compares

patients bone density with peak bone density of a young healthy adult. Z-score compares patients bone density in an age and sex matched adult. As the osteoporosis worsens, the T-score becomes more negative and the fracture risk increases. The WHO criteria for Diagnosis of Osteoporosis is as follows:

Normal: A BMD value of not more than ISD below the young adult mean value (T>-1.0)

Osteopenia: A BMD value that lies between 1 and 2.5 SD below adult mean (-1.0 to —2.5). Such individuals include those in whom the prevention of bone loss would be most useful.

Osteoporosis: A BMD value more than 2.5 SD below the young adult mean value (T<-2.5).

Severe: A BMD more than 2.5 SD below the young adult mean value (T<-2.5) in the presence of one or more fragility fractures.

There are several techniques available for judging bone density. X-rays can show bone loss only when it exceeds 30% or more. Quantitative computer tomography is accurate but is very costly and the radiation exposure is higher. The single photon absorptiometry has low radiation dose but is limited to peripheral skeleton and takes 10-15 minutes scan time. As the isotope has short half life, it requires regular replacement. Ultrasonography though inexpensive is not highly precise and is also limited to peripheral skeleton such as calcaneum. In our study, 56 cases had BMD measurements by sonography as well as DXA. In about one fourth of the cases, osteoporosis was under diagnosed by ultrasonography. At present DXA is considered one of the best techniques as its precision and accuracy are good. It has high resolution and low radiation and can measure all areas, specially the spine and proximal femur. It can be well documented and co-relates to fracture risk and the scan time is less than 5 minutes.

Laboratory evaluation

Biochemical tests can be carried out on blood and urine to estimate the bone turnover. This may also help in evaluating the response to treatment. The higher the bone turnover, the greater the fragility of bones and the possibility of fractures. Serum calcium, serum phosphorous, serum alkaline phosphatase, serum vitamin D3 and DPD/creatinine ratio in urine can be measured. Of 20 cases with osteoporosis, 14 showed significant correlation.

As bone remodelling is dynamic, so is the bio-chemistry dynamic and related to bone resorption. The osteoclasts remove both mineral and organic components of bone and secrete acid and neutral proteases which degrade the collagen fibrils. Due to proteolytic degeneration of Type I collagen, the markers of increased bone turnover are noted. There is decrease in serum calcium and serum phosphorous and increase in serum alkaline phosphates (bone specific). Osteocalcin and Vitamin D3 decrease and derivatives of pyridium crosslinks (Deoxypyidinoline) increase in urine. There is also increase in urinary calcium. DPD is specific of bone resorption and is increased with rapid bone loss. DPD/ Creatinine ratio in urine is therefore used to diagnose the extent of bone resorption.

Hormone Replacement Therapy

Estrogen preserves positive calcium balance by suppressing the bone remodeling rate. It decreases the activation of new remodeling units and thereby suppresses parathyroid hormone mediated bone resorption. The incidence of osteoporotic fractures is 2-3 times greater in women than men because the peak bone mass is lower and there is an accelerated loss after menopause (Melton et al 1992). Progestogens should be administered along with estrogen therapy for all women who have intact uterus. Continuous combined estrogen and progestogen avoids monthly withdrawal bleeding to a considerable extent.

The clinical effects of HRT on preservation of bone mineral density has been proved beyond doubt. However, individualization of treatment, close monitoring and total health care is essential to exert a long term benefit. HRT can be started in the perimenopausal period to treat climacteric and urogenital symptoms and continued for a long time for prevention of osteoporosis and cardiovascular disease. However, for effective prevention, 5 to 10 years is the period recommended.

For maximal skeletal protection, HRT should begin at the time of menopause or oopherectomy. Although it can be initiated any time even later, it slows the rate of bone loss when started in good time and also improves the postural balance and reduces the rate of falling. Compliance is a key issue. Discontinuation of treatment is due to lack of awareness, insufficient counseling, fear of cancer, weight gain and side effects such as breast tenderness, nausea and withdrawal bleeding. The risk and benefits of the therapy have to be understood and as the benefits outweigh the risks, HRT can be given to all, except in cases where estrogens are contraindicated. Alternative therapies can be given in these cases. Several clinical trials have demonstrated the reduction of fracture risk and it is shown that duration of therapy should be as long as possible because the bone mass starts falling again when HRT is stopped. Even older patients who have not received HRT earlier should not be denied treatment. The contraindication for estrogens are history of breast cancer or endometrial cancer, severe liver dysfunction and porphyria. In women with fibroids, endometriosis, migraine, venous thrombosis and familial hypertriglycerdaemia, gallstones, epilepsy and those with increased risk of breast cancer, the clinicians need to be cautious and consider alternative therapies or monitor them very closely.

Felson et al (1993) investigated the effects of 10 years of HRT on BMD in postmenopausal women. After 10 years of therapy, the bone mineral content was significantly higher in the HRT group when compared to those who received no treatment. They noted that women treated for 3 to 4 years had no significant improvement.

Schneider, et al (1997) studied the importance of timing of postmenopausal estrogen for optimal bone mineral density. Estrogen initiated in the early menopausal period and continued into late life is associated with the highest bone density. Nevertheless estrogen begun after age of 60 years and continued appears to offer bone-conserving benefit.

Good nutrition, calcium supplementation, weight bearing exercises and minimising risk factors such as smoking, excessive alcohol and immobilization certainly help. In Mumbai, 70% of women in the upper socio-economic and education strata knew about HRT but among the lower middle class, only 2-5% of women knew about HRT.

HRT Preparations

Estradiol, conjugated estrogens, estradiol valerate, estriol and gonadomimetic preparations such as tibolone (Livial) are used in various formulations, combinations, routes and duration of therapy. The progestogens available for HRT are medroxyprogesterone acetate, norethisterone acetate, lynestrenol and dehydrogesterone. Some clinicians prefer to remove the uterus along with the ovaries in cases of endometriosis leiyomyoma and hyperplasia with irregular bleeding to allow safe HRT. In cases with intact uterus, 72 percent of women achieve amenorrhoea with combined continuous regimen at four months. At one year, 90 percent achieve amenerrhoea (Archer et al. 1994). This certainly improves compliance. However, there is break through bleeding with continuous HRT in 15.8% of women (Leather et al 1991). Tibilone — (Livial) is a gonadomimetic preparation which improves menopausal symptoms including moods and libido and has minimum possibility of vaginal bleeding. The return of endogenic opioids (B endorphins) to premenopausal levels, prevents the vasomotor and psychogenic symptoms. As it is tissue specific, endometrial stimulation and breast tenderness does not occur. It has been shown that there is no increase, rather there is a decrease in mammographic density. It maintains endometrial atrophy in over 95% of postmenopausal women receiving the standard dose of 2.5 mg/day and therefore protects from endometrial cancer.

Progestogens alone may be used in cases of benign breast disease or when estrogens are contraindicated. High doses of progestogens act on the hypothalamus to lower serum gonadotrophins and on the thermoregulatory centre controlling vasomotor symptoms. However, side effects such as irregular bleeding, nausea, edema, weight gain, hair loss and thrombophlebitis are occasionally seen and it is far from the ideal method for prevention of osteoporosis.

Transdermal delivery of estradiol can be done by a skin patch which has the reservoir containing estradiol

dissolved in ethanol and is backed by an occlusive film. These are available in doses delivering 25,50 and 100 ug/24 hr. and can control climacteric symptoms in 80 to 90%. It is effective in reversing genitourinary atrophy and also in preventing osteoporosis. They are particularly useful in women with hypertriglyceridemia, hepatobiliary disorders, venous thrombosis and hypertension. Cyclic progestogens are a mandatory adjunct in non-hysterectomised women.

Subcutaneous estradiol implants have a sustained duration and maintain plasma estrogen levels comparable to those in the follicular phase. They avoid the first pass liver effect and also metabolic derangements (Magos & Studd — 1990.)

Estradiol gel for transdermal use contains 17 B-estradiol, in an alcohol base. It is absorbed through the skin into the systemic circulation and is available in sachets containing 1 mg. of estradiol (Sandrena — Infar). In patients with intact uterus, monthly progestogens in adequate doses and duration should be added.

Transvaginal administration of estrogen, though effective to combat urogenital symptoms is not sufficiently effective to prevent osteoporosis.

Alternative Therapies

Calcium supplements, bisphosophonates, calcitrial, calcitonin, anabolic steroid and sodium fluoride have been tried. Bisphosphonates such as Alendronate have been shown to attenuate bone turnover and specifically inhibit osteoclasts mediated bone resorption. The increase in BMD is maintained during the treatment and for 12 months after the treatment. Liberman et al (1995) reports optimal increase in BMD with 10 mg/day dose and an increase in bone mass of 8.8% at lumbar spine and 5.9% at femoral neck after 3 years of therapy. Addition of Alendronate to ongoing HRT resulted in 5 times greater increase in bone mineral density than HRT alone, in postmenopausal women with low BMD.

Calcitriol deficiency is believed to be significant factor in postmenopausal osteoporosis and its presence is an important regulator of intestinal calcium absorption. Anabolic steroids can be used only for short periods in extreme cases of debility and osteoporosis. Calcium supplements are useful when used along with estrogens in sufficient doses — 1000 to 1500 mg. Vitamin D3 is needed for intestinal calcium absorption. With increased age, the kidney produces less 1,25-dihydroxy vitamin D 9th active form) from Vitamin D. Raloxifen is a selective estrogen receptor modulator (SERM) and has a favourable effect on bone and lipids and does not stimulate endometrium or breast. Alpha D3 is used to regulate mineral metabolism by increasing calcium and phosphate absorption from the intestinal tract well as by mobilizing these minerals from the bones.

These alternative therapies have to be specially considered for women who do not wish to take HRT or when HRT is contra-indicated.

Conclusion

The goals of prevention of osteoporosis is therefore to achieve a high peak bone density at a younger age, have regular physical activity and proper diet and minimise the risk factors for osteoporosis. An awareness of the problem and optimum timing to initiate the treatment and compliance to treatment is necessary. Long term HRT is helpful for prevention of osteoporosis and cardiovascular problems and have additional benefits in minimizing the possibility of Alzhemier's disease. There may be some benefit in prevention of osteoarthritis, diabetes and Parkinson's disease, and in oral health, colon cancer, and age related macular degeneration (AMD) cataracts.

Endometrial cancer can certainly be prevented by addition of progestogens. The risk of breast cancer after 6 to 8 years is known to be very low and some increased risk should be balanced by the expected benefits of better quality of life. Tissue specific HRT such as tibolone is better for cases with higher risks of breast cancer.

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