

AN OVERVIEW OF POSTMENOPAUSAL OSTEOPOROSIS

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SUMMARY

Post-menopausal osteoporosis is a preventable and treatable disorder. It usually comes to attention after its debilitating effects have occurred. There are limited facilities for diagnostic purposes in Pakistan and there have been no epidemiological studies done in this area. Postmenopausal osteoporosis has the potential for becoming one of the leading gynecological problems of Pakistan in the coming decades. The key lies in prevention, tools for early detection and subsequent management of the underlying cause. Physician & patient education is necessary for the preventive aspects which include diet, exercise and hormonal replacement in case of post-menopausal women & endocrine disorders. Appropriate diagnostic equipment with properly trained technicians should be made available for the general population in all tertiary care health facilities.

KEYWORDS: Postmenopausal osteoporosis, hormone replacement therapy

Pak J Med Sci July-September 2004 Vol. 20 No. 3 270-275

INTRODUCTION

Osteoporosis is the outcome of a group of diseases with diverse etiology of which post menopausal variety makes up a significant share. Consensus Development Conference defined osteoporosis as “a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration with a consequent increase in bone fragility and susceptibility to fracture”¹. It has been operationally defined by the WHO as a bone mineral density (T score) that is 2.5 SD below mean peak value of young

adults but this definition is clinically limited. Osteoporosis is not accompanied by a significant change in the ratio of the mineral to the organic phase. It does not exhibit any reproducible abnormality in the structure of organic matrix or the pattern of mineral deposition in the bone. In this condition, both matrix and mineral are lost leading to loss of bone mass and strength. Normally, this is an almost inevitable accompaniment of advanced age. There is a marked tendency to easy fracturing, typically of hip, spine and wrist.

NORMAL BONE STRUCTURE

The general structure of the bone consists of two types of bone tissue².

- * Compact bone, appearing as dense area without cavities.
- * Spongy bone, the bone substance is in the form of slender spicules and trabaculae separated by interconnecting cavities.

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* Received for publication: September 2, 2003

Revision received: April 4, 2004

Revision accepted: April 15, 2004

The three cell types operating in osseous tissue are:

- (i) *Osteoblasts*: These cells are responsible for bone formation. They secrete and synthesize the un-mineralized bone matrix, osteoid and enzyme alkaline phosphate that bring about the mineralization.
- (ii) *Osteocytes*: They are mature bone cells derived from osteoblasts that have secreted bone around themselves. They are connected to each other by cytoplasmic extensions.
- (iii) *Osteoclasts*: They are multinucleated giant cell responsible for resorption of bone by secretion of collagenase and other proteolytic enzymes. They also eliminate debris from bone resorption.

FORMATION AND RESORPTION OF BONE

Remodeling of bone is a continuous process. Any combination of change in rates of bone formation or resorption could cause a decrease or increase in bone mass³. The normal behavior is exaggerated in osteoporosis. In this condition, most studies show that formation rate is normal, although low rates are occasional. Current evidence suggests that in normal individuals, the formation and resorption of bone are tightly coupled and after epiphyseal closure, both rates are normal and nearly equal. However, the rate of remodeling is not uniform through the skeleton after epiphyseal closure. It was proposed that remodeling consists of active units which are characteristically either osteoclastic or osteoblastic in nature and randomly distributed. Resorption precedes formation and is probably more intense, but not lasting as long as formation. Consequently, there are more active formation sites than resorption sites. Unless formation compensates completely for bone resorption, bone mass would have to decrease. After the age of 40-50 years, skeletal mass begins to decline.

The loss has been documented quantitatively using techniques⁴ such as:

1. Radiographic absorptiometry (RA)
2. Single photon absorptiometry (SPA)

3. Dual photon absorptiometry (DPA)
4. Dual energy X-ray absorptiometry (DEXA)
5. Peripheral DEXA
6. Quantitative computed tomography (QCT)
7. Peripheral QCT.
8. Quantitative ultrasound (QUS)

The studies reveal that in most old subjects the resorption rate is higher whereas formation rate is at the same level as that of younger adults. At some critical point, if the difference between the rates of formation and resorption is maintained, loss of bone substance may be so marked that bone can no longer resist the mechanical forces to which it is subjected and fracture results. Now, osteoporosis becomes evident as a clinical problem but the level of reduction in bone mass is sufficient to result in fractures after minimal trauma is variable.

The DEXA scan is most common tool for assessing bone density and 24 hour urine hydroxyproline is the most common method of assessing urinary calcium loss.

Symptoms

1. Chronic backache spread diffusely over whole of the lumbar spine.
2. Loss of height of up to 4-8 inches. Unnoticeable change as it is very gradual.
3. Wedge/Compression vertebral fractures
4. Kyphosis (Dowager's Hump)
5. Colles fractures (perimenopausal)
6. Hip fractures (elderly women)
7. Abdominal distention

Laboratory Findings

1. Biochemistry – see table-I.
2. *Blood Analysis*:
 - (a) Serum Ca level normal (4.5-5.4 mg/L)
 - (b) Serum phosphate level normal (1.45-2.76 mg/L)
 - (c) Serum Alkaline phosphate normal, slightly raised after fracture
3. *Urine Analysis*: Increased excretion of hydroxyproline - an index of bone resorption.
4. *Diagnostic Imaging*: Plain radiography may show fracture or reduction in density.
5. *Histopathology*: Iliac crest bone biopsy shows loss of cancellous bone trabeculae.

Table-I: Biochemical Markers of Osteoporosis
With permission from Eastell et al³²

Bone formation

Serum alkaline phosphatase (bone isoenzyme)
Serum osteocalcin
Serum C- and N-propeptides of type 1 collagen

Bone resorption

Urinary excretion pyridinium cross-links of collagen (e.g., deoxypyridinoline)
Urinary excretion of C- and N- telopeptides of collagen
Urinary excretion of galactosyl hydroxylysine
Urinary excretion of hydroxylysine
Serum tartrate-resistant acid phosphatase

6. (Number and size) with normal width of osteoid seam.
7. *Bone Densitometry*: It shows up to 40% reduction in bone density and osteopenia.

Epidemiology

1. *Prevalence*: 30% of postmenopausal women.
2. *Age*: Predominantly elderly.
3. *Race*: Low prevalence only in Afro-Caribbean.
4. *Genetics*: Significant genetic component in cases with osteoporotic family history^{5,6}.

Risk Factors⁷

Endogenous factors include genetic factors, female gender, Asian, old age, small stature, thin physique, nulliparity, menstrual status: early menopause, previous amenorrhea, endocrine diseases: thyrotoxicosis, hyperparathyroidism, cushing's syndrome, addison's disease, gastro-intestinal diseases: crohn's disease, malabsorption syndromes, etc., rheumatologic diseases and hematological diseases.

Exogenous factors are low calcium intake, reduced physical activity, smoking, alcoholism, surgical menopause and drug therapy: glucocorticoids, anti-epileptics, anti-coagulants.

Etiology of Osteoporosis

1. Idiopathic osteoporosis
2. Endocrine causes
 - Hyperparathyroidism
 - Hyperadrenocorticism
 - Hyperthyroidism
 - Acromegaly
3. Metabolic causes
 - Malnutrition
 - a) Minerals: calcium, phosphate
 - b) Vitamins: vitamin C and D
 - c) Proteins: source of amino acids for collagen
 - Immobilization or prolonged recumbency
 - Primary/Secondary cancers of skeletal system
4. Genetic causes
 - Diabetes Mellitus
 - Osteogenesis Imperfecta
 - Cystic fibrosis
5. Post Menopausal osteoporosis
6. Senile osteoporosis

Pathophysiology

Women are more commonly prone to osteoporosis than men, in a ratio of 4:1, especially after menopause. Estrogens, secreted in women by ovaries, causes increased osteoblastic activity. After menopause, which may be natural or surgical, almost no estrogens are produced. This deficiency leads to:

- * Diminished osteoblastic activity.
- * Decreased bone matrix.
- * Decreased deposition of bone calcium and phosphate

This tendency is also supported by the fact that the bone mass of an adult women is less than that of an adult man of comparative age.

PREVENTION AND TREATMENT

The approach for prevention and therapy is the same. Most of the drugs used decrease bone resorption and are called antiresorptive drugs (Bisphosphonates, HRT, Calcitonin), a misnomer. The following is a list of the modalities recommended for use in osteoporosis:

1. Supplementing calcium orally alone or along with Vitamin D supplementation in high doses has been suggested in different studies^{8,9,10}. Recommended intake is at least 1.2 grams of calcium and 400-800 IU vitamin D daily^{11,12,13}. Calcitriol which is active vitamin D is also being used¹⁴.
 2. Hormonal Replacement Therapy (HRT)^{15,16} has been center of attention for researchers in case of postmenopausal cause. Estrogen replacement, alone or combined with progesterones, after menopause (natural/surgical) has been shown to decrease bone loss associated with osteoporosis. Women's Health Initiative, the largest randomized trial of HRT conducted by NIH, showed that long-term use of HRT poses more risks than benefits. Although estrogen & progesterone arm of the study showed an overall 24% reduction in all fractures and 33% reduction in hip fractures, there was a significant increased risk for coronary heart disease events, invasive breast cancer, stroke, venous thromboembolic events and pulmonary embolism. Therefore, other drugs have taken precedence over HRT for prevention of osteoporosis¹⁷.
 3. Calcitonin is administered either through injection or through nasal spray^{18,19}. It has proven to be more effective when given in combination with calcitriol in case of corticosteroid osteoporosis²⁰. It slows spinal bone loss, increases spinal bone density and reduces pain associated with bone fractures.
 4. Parathyroid hormone replacement has been tried in post-menopausal women²¹. Treatment of postmenopausal osteoporosis with parathyroid hormone (1-34) decreases the risk of vertebral and nonvertebral fractures; increases vertebral, femoral, and total-body bone mineral density; and is well tolerated. The 40- μ g dose increased bone mineral density more than the 20- μ g dose but had similar effects on the risk of fracture and was more likely to have side effects²². Agents that may stimulate the secretion of or mimic PTH activity might also be effective.
 5. Bisphosphonates^{23,24} are stable analogues of pyrophosphate (alendronate, risedronate). They are administered to inhibit osteolytic activity, slow osteoclastic activity and increases bone density. Zoledronate, the most potent of these agents, given IV annually has the same efficacy as daily oral dosing of other bisphosphonates²⁵. Risedronate is specifically used for postmenopausal cases.
 6. Sodium fluoride stimulates bone formation by unknown mechanisms. In one study of 202 women with osteoporosis who were treated with sodium fluoride, lumbar-spine bone mineral density increased by 8 percent per year during all four years of the trial or as a synthetic fragment. Treatment for up to two years results in increased bone mineral density of the spine, but no change is seen in bone mineral^{26,27}.
 7. Raloxifene is a newer agent that is a mixed estrogen agonist-antagonist²⁸ that does not stimulate endometrial growth. It has the same mode of action as estrogen and has provided encouraging results in recent studies^{29,30} and such selective estrogen receptor modulating (SERM) agents like droloxifene, idoxifene and levormeloxifene may replace estrogen replacement in the future.
 8. In a recent study published in 2004, Strontium ranelate has been shown to reduce the risk of vertebral fractures in postmenopausal women in Phase 3 trials³¹. This adds another agent in the list of options now that the role HRT is under review.
 9. Simple physical exercise like brisk walking and stair climbing should be encouraged because regular weight-bearing exercises protect against bone loss.
- However, none of the above modalities is effective on its own and combinations have to be used. Different studies have been carried out in the past decade on the modalities listed above. They are summarized in the table-II.

**Table-II: Treatment approaches to osteoporosis
(With permission from Eastell et al)³²**

<i>Study</i>	<i>Treatment</i>	<i>Dose</i>	<i>No. of Women Duration (Yr)</i>	<i>Comments</i>
Lindsay et al.	Mestranol	25 mg/day	100/Upto 12	Vertebral deformity less common in mestranol group*†
Lufkin et al.	Estradiol (transdermal)	100 mg/day, 21 of every 28 days	75 / 1	Decrease in number of new vertebralfractures†
Storm et al.	Cyclic etidronate	400 mg/day, 2 of every 15 wk	66 / 3	Decrease in number of new vertebral fractures in period from 60 to 150 wk†
Watts et al.	Cyclic etidronate	400 mg/day, 2 of every 13 wk	429 / 2	Decrease in number of new vertebralfractures†‡
Liberman et al.	Alendronate	5–20 mg/day	994 / 3	Decrease in number of patients with new vertebral fractures
Black et al.	Alendronate	5–10 mg/day	2027 / 3	Decrease in number of patients with new vertebral, hip or wrist fractures
Orimo et al.	Alfacalcidol	1 mg/day	61 / 2	Decrease in number of new vertebral fractures§¶
Orimo et al.	Alfacalcidol	1 mg/day	80 / 1	Decrease in number of new vertebral fractures_
Gallagher & Goldgar	Calcitriol	0.5–1 mg/day	50 / 2	No effect on vertebral fractures
Heikinheimo et al.	Vitamin D injection	150,000 to 300,000 IU/yr	341 / Upto 5	Decrease in nonvertebral (especially upper-limb) fractures‡
Tilyard et al.	Calcitriol	0.5 mg/day	622 / 3	Decrease in new vertebral & nonvertebral fractures§¶
Chapuy et al.	Vitamin D (oral) and calcium	800 IU/day and 1200 mg/day	3270 / 1.5	Decrease in number of patients with hip fractures
Dawson- Hughes et al.	Vitamin D (oral) and calcium	700 IU/day and 500 mg/day	389 (men & women)/3	Decrease in number of patients with nonvertebral fractures
Lips et al.	Vitamin D (oral)	400 IU/day	2578 / Upto 3.5	No decrease in number of patients with hip fractures
Reid et al.	Calcium	1000 mg/day	86 / 4	Decrease in number of patientswith new nonvertebral fractures_
Recker et al	Calcium	1200 mg/day	197 / 4.3	Decrease in number of patients with new vertebral fractures among those with vertebral fractures at base line
Overgaard et al.	Calcitonin (intranasal)	50–200 IU/day	208 / 2	Decrease in number of new vertebral fractures_
Rico et al.	Cyclic calcitonin (intramuscular)	100 IU/day, 10 of every 30 days	72 / 2	Decrease in number of new vertebral fractures§
Mamelle et al.	Sodium fluoride	50 mg/day	257 / 2	Decrease in number of new vertebral fractures§¶
Riggs et al.	Sodium fluoride	75 mg/day	202 / 4	No effect on vertebral-fracture rate, but increase in non vertebral-fracture rate
Meunier et al.	Sodium fluoride or Monofluoro-phosphate	50 mg/day or 150–200 mg/day	354 / 2	No effect on rate of vertebral or nonvertebral fracture
Kleerekoper et al.	Sodium fluoride	75 mg/day	84 / 4	No effect on rate of vertebral or nonvertebral fracture
Pak et al.	Cyclic sodium fluoride (slow-release)	50 mg/day, 12 of every 14 mo	110 / Up to 5	Decrease in number of patients with new vertebral fractures§
Lindsay et al.	Parathyroid hormone	400 U/day	34 / 3	Decrease in vertebral deformities_

* There were no spine radiographs at base line, so vertebral morphometry was cross-sectional.

†The extension study was uncontrolled.

‡ The treatment groups were pooled.

§The study was not blinded.

¶ The study had no placebo group.

_ The number of women with fractures was small (<10).

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