ABSTRACT
Osteoporosis is far the most common metabolic bone disease. Bone mineral density, dual energy X-ray absorptiometry (DEXA) has become standard method for determining bone marrow density. By measuring BMD, it is possible to predict fracture risk in the same manner that measuring blood pressure can help predict the risk of stroke. Approximately 10 -15% of patients with osteoporosis fail to respond to treatment. As in most chronic diseases, compliance is usually poor in patients on long term treatment of osteoporosis. Thus, the aim of monitoring should be to increase adherence to treatment as well as to ascertain response to treatment. Because fracture events are uncommon, they cannot be used to monitor drug effectiveness. Repeat BMD measurement especially at the spine, is recommended once every two years to confirm treatment response.

Key Words: Osteoporosis, Bone mineral density, dual energy X-ray absorptiometry.

INTRODUCTION
Osteoporosis is far the most common metabolic bone disease. Bone quality and strength cannot be measured easily. Bone Mineral Density (BMD) is the parameter that can be determined best in-vivo. It has high precision and it correlates well with the biomechanically determined bone strength. Because Bone mineral density is a partial predictor of bone strength and a powerful predictor of fractures1,2, an operational definition of osteoporosis was developed by a study group of the W.H.O. that empirically defined osteoporosis as a BMD that is >2.5 S.D. below peak bone mass. (Mean BMD that a young healthy adult of the same gender achieves at any age)3. These categories are clearly arbitrary but do give some indication of fracture risk. Currently diagnostic categories for post menopausal women are based on measurements of BMC4. However the risk of fracture at any given BMD increased markedly with age and can be affected by a number of other factors5.

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>DEFINITION</th>
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</thead>
<tbody>
<tr>
<td>Normal</td>
<td>A value of BMD or BMC &gt;-1 S.D. of the young adult reference mean</td>
</tr>
<tr>
<td>Low Bone Mass (Osteopenia)</td>
<td>A value of BMD or BMC &lt;-1 S.D. and &lt;2.5 S.D. lower than the young adult reference mean</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>A value of BMD or BMC &gt;-2.5 S.D. lower than the young adult reference mean</td>
</tr>
<tr>
<td>Severe Osteoporosis (Established Osteoporosis)</td>
<td>A value of BMD or BMC &gt;-2.5 S.D. lower than the young adult reference mean in the presence of one or more fragility fractures</td>
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</table>

A value of BMD or BMC >-2.5 S.D. lower than the young adult reference mean in the presence of one or more fragility fractures. It is noteworthy to mention that this BMD diagnostic threshold applies only to post-menopausal Caucasian women and only to DEXA measurements6. Such a cut-off identifies 30% of post-menopausal Caucasian women as having osteoporosis using measurements done at spine, hip and forearm. This percentage is equivalent to the lifetime risk of fractures at these sites6. T-score has several limitations, in view of the presence of other independent powerful predictors of fractures. A more rational approach to diagnosis and treatment might be to obtain an estimate of fracture risk based on all fractures in individual patients. The use of T-scores to categorize BMD measurements as indicating the presence or absence of osteoporosis is complicated by the fact that the estimation of fracture risk is both site and method specific7. Indeed because of age and prevalent fractures are independent risk factors for future fractures, there is a need to move towards absolute 5 or 10 year fracture risk using age, BMD and other traditional factors such as BMC and history of prevalent fractures8. As for example, 10 year probability for sustaining any osteoporotic fracture, i.e., hip, shoulder or vertebral fracture for a 50 year old woman with a T-score of -2.5 at the hip is estimated at 11.3% such estimate increases to 16.2% in a 60 year old woman, to 22.8% in a 70 year old woman, and to 25.6% in a 80 year old woman8.

Figure 1– T Scores

References:
1. Dr. Ramesh Narula, Associate Professor, Department of Orthopedics, Rohilkhand Medical College, Bareilly, UP-243006, India.
2. E-mail: rameshnarula55@gmail.com
3. Article Received on: 11/07/12 Revised on: 10/08/12 Approved for publication: 04/09/12
SYMPTOMS AND SIGNS
Usually, osteoporosis does not cause any symptoms at first. Osteoporosis is often called the "silent" disease, because bone loss occurs without symptoms. People often don't know they have the disease until bone breaks, frequently in a minor fall that wouldn't normally cause a fracture such as bending over, lifting, jumping, or falling from the standing position. The fragility fractures can cause severe back pain, but sometimes they go unnoticed—either way, the vertebrae collapse down on themselves, and the person actually loses height. The hunchback appearance of many elderly women, sometimes called "dowager's" hump or "widow's" hump, is due to this effect of osteoporosis on the vertebrae. People with osteoporosis may break other bones, particularly the hip and wrist. Hip and wrist fractures often occur after a fall. A broken hip is especially serious. It can lead to loss of independence and function and to serious, even life-threatening problems. However, all broken bones in people with osteoporosis are serious, because bones that are less dense tend to heal slowly and sometimes incompletely. Also, if people with osteoporosis break one bone, they tend to break other bones. Patients with uncomplicated osteoporosis may be asymptomatic or may have pain in the bones or muscles, particularly of the back.

CONSEQUENCES / COMPLICATIONS
The consequences of osteoporosis are financial, physical, and psychosocial, which significantly affect the individual as well as the family and community. Osteoporosis bone fractures are responsible for considerable pain, decreased quality of life, lost workdays, and disability. Notably, one in five patients is no longer living 1 year after sustaining an osteoporotic hip fracture. The impact of osteoporosis on other body systems, such as gastrointestinal, respiratory, genitourinary, and craniofacial, is acknowledged, but reliable prevalence rates are unknown. Fear, anxiety, and depression are frequently reported in women with established osteoporosis and such consequences are likely under-addressed when considering the overall impact of this condition. Between 14% and 36% of women who experience a hip fracture die within a year afterward and about 25% require nursing home treatment. The mortality rates after major fractures may be even higher in older men than in older women. The lower survival rates after major fractures are generally associated with poor general health. In fact, one 1999 study suggested that tiny spinal fractures in older female patients (even some that may go unnoticed by physicians) may be associated with serious illnesses, including lung disease and cancer. For example, kyphosis, which occurs with severe osteoporosis, puts pressure on the lungs and is probably the major factor in the higher rates of death from lung disease among patients with osteoporosis.

MEASUREMENT OF BONE MINERAL DENSITY
By measuring BMD, it is possible to predict fracture risk in the same manner that measuring blood pressure can help predict the risk of stroke. It is important to remember that BMD cannot predict the certainty of developing a fracture. It can only predict risk. Low bone density at the measured areas of the spine and hip can even predict future osteoporotic fractures at other parts of the body besides the spine and hip. In subjects with a BMD in the osteoporosis range, there is approximately a 5 times increase in the occurrence of osteoporotic fractures. Measurements of BMD are given as mg/cm2, which is the average concentration of bone mineral in the areas that are scanned with the imaging tests. In general, normal bone is greater than 833 mg/cm2. Low bone density (Osteopenia) is between 833 and 648 mg/cm2. Osteoporosis is lower than 648 mg/cm2.

Dual Energy X-ray Absorptiometry (DEXA) has become standard method for determining bone mineral density. It uses two x-ray beams, a second energy beam to correct for absorption of x-ray energy in non-calcium-containing tissues. It based on the fact that radiations of distinct energies are attenuated by tissues to different extents. DEXA scanners provide either pencil or fan beam techniques. Fan beam techniques are faster. There are two different types of DEXA scanning devices, central and peripheral. Central devices measure BMD at hip and spine. These have a large flat table and an arm suspended overhead. There are small DXA scanners called peripheral DXA machines (pDEXA). Peripheral DEXA devices measure bone density at wrist, heel or fingers. These are small portable devices which are less expensive. Regular DXA machines have a standard reference (called NHANES III) that can be used for all machines no matter who the manufacturer is. However, peripheral DXA machines do not yet have a uniform reference standard for the normal peak young adult bone mass that can apply to all machines and all manufacturers. This is necessary for peripheral DXA to be ready for more widespread use. Efforts are in progress to make the peripheral DXA technique more standardized. The limitations of this technique are:

- The mechanical strength of the vertebrae is mainly dependent on the amount of trabecular bone in the vertebral body. In conventional AP projection of the spine the posterior elements, which consist of cortical bone are included in the result. Lateral DEXA has been suggested as it can focus on vertebral bodies only but superimposition of pelvis and hip limit exposure up to L3 only.
- Vertebræ with larger size have a higher BMD.
- Soft tissue calcification in the adjacent area may lead to falsely increased BMD.
- Degenerative changes like osteophytes in the elderly may also lead to falsely increased BMD.

Despite the above limitations, the low radiation doses, speed of examination, and low cost have made it popular for measuring BMD. The imaging of proximal femur is more technically demanding. The regions of interest (ROI) are the neck region, the trochanteric region and the intertrochanteric region. The Ward’s ROI is a square of 1*1 cm with the lowest density in the proximal femur. Precision of hip BMD is less than that of spine. Correct positioning by internal rotation of the hip with straight femoral shaft is essential to avoid error in measurement, making it technically demanding. Osteoarthritis, Paget’s disease, fracture, vascular calcification, calcific tendonitis, and avascular necrosis are also potential sources of error. The BMD measurement is interpreted in two forms: T-score: It shows the amount of BMD compared with a young adult of the same gender with normal peak young adult bone mass that can apply to all machines and all manufacturers. This is necessary for peripheral DXA to be ready for more widespread use. Efforts are in progress to make the peripheral DXA technique more standardized. The limitations of this technique are:

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Absorptiometry (SPA), Dual Photon absorptiometry (DPA), Single X-ray Absorptiometry (SXA).

**Quantitative computed tomography (QCT)**

QCT allows for a true three dimensional BMD measurement (mg/cm³) without superimposition of other tissues and which is not influenced by the bone size. It reliably excludes extra-osseous calcifications like aortic sclerosis and plaques, ligament calcification and osteophytes that can influence DEXA. One major disadvantage of QCT is that it artifacts hamper the CT data, reducing its accuracy. Another disadvantage is that it is more costly and it uses radiation doses significantly higher than that of DEXA.

**Quantitative Ultrasound**

It is used primarily for peripheral sites. Its advantages are low cost, portable device and no ionizing radiation dose. These provide a relative risk comparable to bone density measures in hip fracture and vertebral fractures. The clinical issues associated with the reliability and reproducibility of the ultrasound measures includes reproducible placement of transducers and temperature variations of the foot. It can be used for the screening purpose for osteoporosis.

**Magnetic resonance imaging (MRI)**

Most widely used application of MRI in the diagnosis of osteoporosis is not in the quantization of bone mass but in the detection of osteoporotic bone fractures. It can document radiologically occult fractures common in the elderly. Another important application is differentiation between vertebral body fractures caused by osteoporosis and those caused by metastasis. In case of metastatic fractures the signal of the entire bone marrow of a vertebral body is changed. Osteoporotic fractures often show isolated band like signal changes parallel to the cortical end plates with preservation of normal marrow signal in the non-deformed portions of the vertebrae. Recently, the capabilities of Quantitative Magnetic Resonance (QMR) and Magnetic Resonance Microscopy (MMR) have been explored for assessing osteoporosis in specific cases.

Who should have bone density testing? At present, the National Osteoporosis Foundation and the U.S. Preventive Services Task Force the two most prominent guidelines about BMD testing; have recommended that all women over the age of 65 be tested, regardless of risk factors. The guidelines differ a little bit regarding younger women because of the lack of reliable scientific information. However, in general, testing is recommended for all postmenopausal women between the ages of 50 and 65 years who have risk factors for osteoporosis other than menopause. These include history of vertebral compression fractures, fragility fracture after the age 40 years, family history of fracture (especially maternal hip fractures), prolonged systemic steroid therapy, low body weight, low physical activity, excessive cigarette smoking, malabsorption syndrome, primary hyperparathyroidism, low dietary calcium intake, excessive alcohol intake, chronic anticonvulsant therapy, long term heparin therapy, excessive caffeine intake, rheumatoid arthritis, history of clinical hyperthyroidism.

BMD is not mandatory for postmenopausal women with fractures because treatment may well be started regardless of bone density. It is also advised that anyone seeking therapy for osteoporosis be tested. These are guidelines only, and it should be remembered that testing is only indicated if it will influence treatment decision. For example, is the person willing to be treated if the results indicate an increased fracture risk?

**Radiographic assessment in osteoporosis (X-RAYS)**

Conventional radiographs are relatively insensitive for demonstrating osteoporosis because it takes a bone loss of 20 – 40% before osteoporosis is visualized on x-rays. Features of osteoporosis are more prominent in axial skeleton than anywhere else. General features of osteoporosis in radiographs are increased radiolucency, decreased number and increased thickness of trabeculae, cortical thinning, juxta-articular osteopenia with trabecular prominence, bone bars (reinforcement lines) and pathological fractures. In spine, especially in lower dorsal and lumbar region, there is accentuated primary trabecular pattern, picture framing of vertebral bodies, biconcave bodies and compression fractures (concertina collapse). Important differential diagnosis on conventional radiographs are osteomalacia, hyperthyroidism, renal osteodystrophy, malignant bone diseases e.g. plasmacytoma, diffuse metastatic disease. The differential diagnosis of osteoporotic and metastatic pathologic fracture may be difficult. Fractures located above T7 level, associated with soft tissue mass or osseous destruction and involving the posterior elements are most likely malignant.

Various indices have been described for diagnosting the severity of osteoporosis i.e. Saville index, Singh’s index, Jhamaria-Lal or Calcaneal Index.

**Table 2- Saville Index**

<table>
<thead>
<tr>
<th>GRADE</th>
<th>Radiographic Appearance of vertebra</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal bone density.</td>
</tr>
<tr>
<td>1</td>
<td>Minimal loss of density; end plates begin to stand out giving a stenciled effect.</td>
</tr>
<tr>
<td>2</td>
<td>Vertical striation more obvious; end plates are thinner.</td>
</tr>
<tr>
<td>3</td>
<td>More severe loss of than grade 2; end plates becoming less visible.</td>
</tr>
<tr>
<td>4</td>
<td>Ghost like vertebral bodies; density is not greater than soft tissues; no trabecular pattern is visible.</td>
</tr>
</tbody>
</table>

**Table 3- Singh’s Index**

<table>
<thead>
<tr>
<th>GRADE</th>
<th>Radiographic Appearance of proximal femur</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>All normal trabecular groups are visible. Upper end of femur appears to be completely occupied by cancellous bone.</td>
</tr>
<tr>
<td>5</td>
<td>Principal tensile and principal compressive trabeculae are accentuated. Ward’s triangle appears prominent.</td>
</tr>
<tr>
<td>4</td>
<td>Principal trabeculae are markedly reduced but can still be traced from lateral cortex to upper part of femoral neck.</td>
</tr>
<tr>
<td>3</td>
<td>There is a break in the continuity of the principal tensile trabeculae opposite the greater trochanters. This grade indicates definite osteoporosis.</td>
</tr>
<tr>
<td>2</td>
<td>Only principal compressive trabeculae stand out prominently. Remaining trabeculae have essentially been absorbed.</td>
</tr>
<tr>
<td>1</td>
<td>Principal compressive trabeculae are markedly reduced in number and are no longer prominent.</td>
</tr>
</tbody>
</table>

**Table 4- Jhamaria-Lal / Calcaneal Index**

<table>
<thead>
<tr>
<th>GRADE</th>
<th>Radiographic Appearance of Calcaneum</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Normal trabecular pattern.</td>
</tr>
<tr>
<td>4</td>
<td>The posterior compression trabeculae are divided into two pillars separated by a radiolucent area due to recession and disappearance of the middle portion.</td>
</tr>
<tr>
<td>3</td>
<td>Recession and disappearance of the posterior tensile trabeculae which now cross only the anterior pillar of the posterior compression trabeculae.</td>
</tr>
<tr>
<td>2</td>
<td>The anterior tensile trabeculae have disappeared and the posterior tensile trabeculae have receded.</td>
</tr>
<tr>
<td>1</td>
<td>There is complete disappearance of both sets of tensile trabeculae: the compression trabeculae are reduced in number and are thin.</td>
</tr>
</tbody>
</table>
Radiogrammetry is a semi-quantitative method of bone mineral analysis in which measurements are derived from radiographs most commonly through determination of metacarpal index (MCI). MCI is measured from hand radiographs as the ratio between cortical thickness and total bone width in the mid diaphysis of at least two metacarpal bones. This method is useful in measuring the bone mineral content in appendicular skeleton but is of limited clinical content in appendicular skeleton but is of limited clinical usefulness because most of the metabolic changes associated with osteoporosis are complete cures. In other words, it is difficult to completely rebuild bone that has been weakened by osteoporosis. Therefore, prevention of osteoporosis is as important as treatment. Osteoporosis treatment and prevention measures are:

A. Orthopedic management of fractures: Early surgical management of fractures especially hip fractures is essential to decrease mortality rate and to improve perioperative morbidity. The healing of a fracture although the fracture has healed, the risk of subsequent fracture remains. Many studies have shown that local osteoporosis affects anchorage of implants and needs special attention regarding the implants and techniques used for fixation. The poor quality of trabecular network requires adequate fixation elements and at the same time the needs special attention regarding the implants and techniques used for fixation. The poor quality of trabecular network requires adequate fixation elements and at the same time the quality of trabecular network requires adequate fixation elements and at the same time the development of bone loss (although it is not associated with any risk for fracture).

ROLE OF SERUM 25-HYDROXY VITAMIN D IN OSTEOPOROSIS

The Indian subcontinent has adequate sunshine throughout the year. Thus, it has been presumed that Indians are vitamin D sufficient. Using a serum 25(OH) Vitamin D level of 15 ng/ml as a cutoff, in a study by Arya et al 66.3% (61/92) of the subjects were found to be vitamin D deficient. Of these, 20.6% (19/92) subjects had severe vitamin D deficiency (<5 ng/ml). When a serum 25(OH) Vitamin D level of 20 ng/ml was used as a cutoff, 78.3% subjects were diagnosed to be vitamin D deficient/insufficient. The serum 25(OH) Vitamin D level correlated with BMD at the femoral neck and Ward's triangle (r=0.50, P=0.020 and r=0.46, P=0.037, respectively). The findings show that vitamin D deficiency is common in urban north Indians. The possible reasons include inadequate sunlight exposure and skin pigmentation in Indians. A low serum 25(OH) D level is possibly one of the reasons for lower bone mineral density among Indians. Various other studies have demonstrated that vitamin D deficiency is fairly common in the Indian subcontinent and that a low serum 25OHD level was also associated with higher serum alkaline phosphatase and lower Bone Mineral Density. Bart Seamier et al demonstrated that assays for routinely used bone biochemistry parameters including serum calcium, phosphate, Parathormone and alkaline phosphatase are not representative of hypovitaminosis D even in those whose serum PTH is elevated and only reliable way to confirm this is to do vitamin D levels.

MANAGEMENT OF OSTEOPOROSIS

The goal of osteoporosis treatment is the prevention of bone fractures by stopping bone loss and by increasing bone density and strength. Although early detection and timely treatment of osteoporosis can substantially decrease the risk of future fracture, none of the available treatments for osteoporosis are complete cures. In other words, it is difficult to completely rebuild bone that has been weakened by osteoporosis. Therefore, prevention of osteoporosis is as important as treatment. Osteoporosis treatment and prevention measures are:

A. Orthopedic management of fractures: Early surgical management of fractures especially hip fractures is essential to decrease mortality rate and to improve perioperative morbidity. The healing of a fracture in osteoporotic bone passes through the normal stages and concludes with union of the fracture although the healing process is prolonged. The problem lies with the increased risk of fractures and the poor fixation and anchorage of fracture. Many studies have shown that local osteoporosis affects anchorage of implants and needs special attention regarding the implants and techniques used for fixation. The poor quality of trabecular network requires adequate fixation elements and at the same time the number and size of implants that can be placed, especially in
the articular fragment, is often limited. Currently research is progressing on three different approaches to address the problem of fractures of the osteoporotic bone:

1. Adapted anchoring techniques like angled blade plate, trochanteric stabilization blade, spiral blade plate, anchoring screws with non-cutting threads, intramedullary rod with crossed nails, dynamic hip screws and Mennen plate. Blade provides a broad surface contact area perpendicular to the main loading axis within metaphyseal bone capable of resisting considerable torsion and bending movements. A modification of the existing lag screws of DHS has been introduced with spiral thread geometry, which compresses the cancellous bone rather than cutting it. Trochanteric stabilization plates are indicated in unstable fracture patterns and they prevent lateral displacement of greater trochanter. Intramedullary fixation is especially useful in osteoporotic fractures as the central location of the implant endures more uniform distribution of loads. Mennen plate having fastening arms formed on at least two edges of the plate has been used for treatment of periprosthetic femoral diaphyseal fractures.

2. Improved Load Distribution: Locking compression plates and metaphyseal plates with locking screws. Locking screws have a better purchase in osteoporosed bones. In locking compression plates, the interlocking of the screws within the plate allows minimization of bone implant contact and thus less deleterious effect on the vascularity; at the same time it provides a rigid construct as there is no toggle at the plate screw interface.

3. Augmentation with bone substitutes. Fenestrated screws are available so that cement can be injected to augment the hold of screw threads into the bone. Coating of screws with materials like hydroxyapatite and bisphosphonates have shown to provide better fixation in bone and higher pullout strength in experimental studies. BMP-2, TGF-b, FGF etc. are under consideration. PMMA bone cement or synthetic bone substitutes can be used to augment the fixation and support the subchondral bone during fixation of juxta-articular fractures especially distal end radius and proximal tibia.

**B. Pharmacological measures:**

1) Calcium and Vitamin D Supplementation: Calcium and vitamin D decrease bone loss and risk of fracture at all ages, especially in elderly. They are however, usually not used as sole treatment of osteoporosis but as essential adjuncts to treatment. Although calcium in the form of dairy products is as effective as calcium supplementation, supplementation is necessary in most cases to achieve an adequate calcium intake. Findings of some studies suggest a reduction in the frequency of fractures in the patients who receive calcium supplementation. Patents should always take calcium tablets with food, as it increases absorption because the grinding of food breaks it up. Calcium preparations that are chewed are automatically bioavailable. Calcium intake is associated with mild gastrointestinal upsets like constipation.

2) Bisphosphonates: are the most widely studied and first line drugs in post-menopausal and corticosteroid induced osteoporosis. Alendronate, Risedronate and Ibudronate are currently approved by FDA for use in osteoporosis. Bisphosphonates bind avidly to mineralized bone surfaces and reduce osteoclastic bone resorption. Nitrogen containing bisphosphonates inhibit mevalonic acid pathway resulting in decreased osteoclast recruitment and activity and decreased rate of remodeling. Non-nitrogen containing compounds produce cytotoxic analogues of ATP, increasing osteoclast death. The net result is increased BMD and decrease in bone turnover markers. As bisphosphonates persist in the skeleton for many months, their duration of action is prolonged beyond the period of administration. For optimum effectiveness of bisphosphonates adequate intake of calcium and vitamin D and weight bearing and muscle strengthening exercises are important. They are poorly absorbed and oral bioavailability is 1 - 3 %. Absorption is further impaired by food, calcium, iron, coffee, tea, orange juice etc. They should, therefore, be taken first thing in the morning and patient should not take anything orally and remain upright for at least 30 minutes. These compounds are quickly cleared from the plasma. 50% is deposited in bone and 50% excreted in urine. Their half life in bone is several years. Most common side effects are dyspnoea, abdominal pain and diarrhea.

3) Hormone Replacement Therapy (HRT): Oestrogen deficiency is associated with increased secretion of cytokines resulting in the recruitment and activation of more osteoclasts, which leads to increased bone resorption. Oestrogen therapy reverses this process within 4 weeks. In the WHI trial HRT reduced the risk of vertebral fractures by 34% and of all other osteoporotic fractures by 24%. After 3 years treatment, total hip BMD was increased by 3.7% as compared to 0.14% in the placebo group. Meta-analysis of various randomized trials suggests a 33% reduction in vertebral and 27% reduction in non-vertebral fractures [94, 95]. HRT was earlier considered an effective antiresorptive agent for preventing post-menopausal bone loss. However, overall results show that health risks outweigh these benefits. Women Health Initiative (WHI) and the Million Women Study (MWS) studies have confirmed that HRT does not reduce the risk of coronary Heart Disease and increases the risk of breast cancer, stroke and deep vein thrombosis. As a result of these findings other antiresorptive agents are now the drug of choice for post-menopausal osteoporosis. Use of HRT is presently limited to post-menopausal women with severe hot flushes, and vaginal and skin changes. It should be used for the shortest time possible, at a dose as low as possible in order to stop post menopausal symptoms (hot flushes) and only when benefits outweigh risks. In women with intact uterus progestins should be added in combined cyclic regimen for women close to menopause and in continuous regimen especially in women more than five years post-menopausal to decrease the risk of endometrial cancer.

4) Selective Estrogen Receptor Modulators (SERMs): are estrogens like compounds that bind with high affinity to the estrogen receptors and could have either estrogen agonist or antagonist activity. Raloxifene is the first of the second generation SERMS and the only one approved for prevention and treatment of osteoporosis. It has agonist action on skeleton and antagonist action on breast and endometrium. It therefore, minimizes the undesirable effects of estrogens. Apart from the skeletal effects raloxifene induces a dose dependent decrease of serum total cholesterol and LDL and may reduce the risk of cardiovascular events especially in women with increased cardiovascular risk at baseline. Two others SERMs to be discussed are Tamoxifen and Tibolone. Tamoxifen increases the risk of endometrial cancer precluding its use in osteoporosis. Tibolone is a synthetic steroid that acts on estrogen, progesterone and androgen receptors either directly or indirectly through its metabolites, with a different pattern according to the target tissue. It prevents bone loss in early and late post-menopausal women but its effect on fracture risk has not been investigated. Its
overall effect on other tissues and its safety needs to be studied in large long term placebo controlled studies.

5) Calcitonin: It is polypeptide hormone produced by thyroid C-cells, and reduces bone resorption by direct inhibition of osteoclastic activity. Salmon calcitonin nasal spray 200 IU/d is approved for the treatment of postmenopausal osteoporosis. Fracture data are available from 1 major clinical trial, the 5-year Prevent Recurrence of Osteoporotic Fractures (PROOF) study. It significantly reduced morphometric vertebral fracture risk by 33% (P = 0.03), whereas vertebral fracture risk was reduced by 15% and 16% in the 100- and 400-IU/d groups, respectively (both not significant). The lack of a dose-response effect in this study has raised some concerns about the reliability of the data. The 5-year risk of hip and nonvertebral fractures was not significantly reduced. Calcitonin should always be accompanied by optimum calcium and vitamin D intake / supplementation. Calcitonin is less effective in reducing cortical bone loss than cancellous bone loss in post-menopausal women. Treatment with calcitonin should be considered in older women with osteoporosis on multiple medications or those who fail to tolerate / respond to other medications. It is of special importance in acute vertebral fractures because of its unique analgesic effect. Salmon calcitonin given 200 IU/d in alternate nostrils was generally well tolerated in the PROOF study. Rhinitis was the most commonly reported adverse event, occurring in 22% of active drug recipients and in 15% of placebo recipients (P < 0.01). The possibility of an allergic reaction should also be considered, and patients suspected of having an allergy to salmon calcitonin should undergo skin testing before treatment. Other side-effects are facial flush, nausea and vomiting.

6) Parathormone (PTH) / Teriparatide (rhPTH): Parathormone is an anabolic agent that acts by stimulating bone formation. Continuous exposure to high dose PTH increases osteoclast differentiation and action leading to bone resorption. On the contrary intermittent injections of low dose PTH produces increase in osteoblast number and function leading to bone formation, thickening the cortices and existing trabeculae of the skeleton, and perhaps increasing trabecular numbers and their connectivity. Teriparatide is a recombinant form of human parathyroid hormone approved by the FDA for treatment of osteoporosis in postmenopausal women who are at high risk for fracture. Fracture data for teriparatide are available from 1 major clinical trial. The study was terminated early to investigate reports of osteosarcoma in rats during a long-term toxicological study. Once-daily teriparatide 20 mcg/d, given subcutaneously, significantly reduced the risk of new morphometric vertebral fractures by 65% after a median follow-up of 21 months. The corresponding reduction for the 40 mcg/d dosage was 69% (P = 0.001). The number of hip fractures was too small to provide a meaningful analysis. Teriparatide 20 mcg/d significantly reduced the risk of nonvertebral fragility fractures by 53%. A similar reduction (54%) was observed in the 40 mcg/d group. Side effects include transient dose-dependent mild hypocalcaemia and hyperuricemia within 4-6 hours. The incidences of or leg were slightly higher in the teriparatide 20 mcg/d group than in the placebo group. The incidences of nausea or headache were significantly higher. This anabolic agent is especially indicated in patients with severe osteoporosis with high risk of fractures and older patients with osteoporosis. The benefits of PTH persist when antiresorptives are maintained. The product label for teriparatide includes a black box warning for patients at risk for osteosarcoma, and use of teriparatide for more than 2 years is not recommended. The clinical relevance of the rat data that led to the early termination of the above study is uncertain given the long duration of therapy (80-90% of the normal life span of the rats being tested) and the suprapharmacologic dosages used (rats were treated for about 25-30 bone turnover cycles compared with 1-3 bone turnover cycles for postmenopausal women).

Comparative Studies: In a number of head-to-head studies, alendronate has demonstrated greater improvements in BMD and greater reductions in markers of bone turnover than estrogen, risedronate, raloxifene, and salmon calcitonin nasal spray. A small study (n = 146) comparing the effects of teriparatide versus alendronate in postmenopausal women with osteoporosis reported effect on BMD and fracture risk. Teriparatide 40 mcg/d produced significantly greater increases in lumbar spine, femoral neck, and total hip BMD than alendronate 10 mg/d (median follow-up 14 months). The incidence of nonvertebral fractures was significantly lower in the teriparatide than in the alendronate group (4.1% versus 13.7%; P = 0.042). This small study was not specifically designed to compare fracture rates, and therefore, it is difficult to draw any firm conclusions regarding the relative efficacy at reducing fracture risk for these agents. Moreover, there are data to suggest that changes in BMD with antiresorptive agents account for only a small proportion of the observed vertebral fracture risk reductions. Therefore, head-to-head fracture trials would be needed to definitively determine relative antifracture efficacy between agents.

Combination Therapies: The issue of combination therapy with parathyroid hormone plus antiresorptive drugs is of particular interest. Many patients who are candidates to receive parathyroid hormone therapies like teriparatide are currently receiving antiresorptive drugs. To date, there is no fracture data for combination therapy. In a 30-month study of 83 men with low BMD, the increase in lumbar spine and femoral neck BMD was significantly greater in patients who received teriparatide monotherapy than in those who received either alendronate monotherapy or teriparatide plus alendronate combination therapy (patients received alendronate for 6 months, then concurrent alendronate and teriparatide for 24 months). Similarly, the anabolic effects of parathyroid hormone were reduced by concomitant administration of alendronate in a study of 238 previously untreated women with postmenopausal osteoporosis. There are data to suggest that raloxifene is associated with less blunting of the anabolic effect of teriparatide than alendronate, which may be due to the lower antiresorptive potency of the former. The effects of starting antiresorptive therapy after parathyroid hormone treatment have also been evaluated. In a follow-up study, 119 women receiving parathyroid hormone monotherapy had their treatment stopped and then received either alendronate or placebo for 1 year. Gains in spine and hip BMD were quickly lost during the year on placebo, and there were significant gains in the alendronate group. These data suggest that treatment with an antiresorptive agent is needed after discontinuation of parathyroid hormone therapy to maintain the drug-induced improvements in BMD.

Treatments on the Horizon: Strontium ranelate: is an orally active drug that has recently completed phase III Clinical trials. It acts by inducing uncoupling in the bone remodeling process, preventing osteoclasts from resorbing the bone and at the same time also promoting osteoblasts to make new bone. The Spinal Osteoporosis Therapeutic
Intervention (SOTI) trial in 1,649 postmenopausal women with osteoporosis reported a 49% (P < 0.001) reduction in new morphometric vertebral fractures with strontium ranelate 2 g/d relative to placebo after 1 year, and a 41% (P < 0.001) reduction over 3 years. Similar reductions in vertebral fracture risk were observed in the Treatment of Peripheral Osteoporosis (TROPOS) study. In addition, the TROPOS study showed that treatment with strontium 2 g/d significantly reduced the risk of all nonvertebral fractures by 16% (P = 0.04) and of major nonvertebral fragility fractures (hip, wrist, pelvis and sacrum, ribs and sternum, clavicle and humerus) by 19% (P = 0.031) in 4,932 postmenopausal women with osteoporosis. The most commonly reported adverse event for strontium in the SOTI study was diarrhea. In the TROPOS study, nausea, diarrhea, headache, dermatitis, and eczema were reported more frequently (not significant) in strontium than placebo recipients. In both studies, the differences in diarrhea and nausea between strontium and placebo disappeared after 3 months.

Zoledronic acid: use of for the treatment of postmenopausal osteoporosis is appealing because of its extended dosing interval. Phase III trials are in progress. No fracture data is available. In a 1-year dose-ranging BMD study in 351 women with postmenopausal osteoporosis, patients who received any of 5 dosing regimens of i.v. zoledronic acid (0.25 mg every 3 months, 0.5 mg every 3 months, 1 mg every 3 months, 2 mg every 6 months, or 4 mg * 1 dose) had significantly greater increases in lumbar spine (range 4.3% - 5.1% higher) and femoral neck (range 3.1% - 3.5% higher) BMD than patients who received placebo. Musculoskeletal pain (10-20% of patients), fever (9-20%), and arthralgia (8-25%) were commonly reported in zoledronic acid recipients.

Growth Hormone: has been used in the treatment of osteoporosis because of its anabolic effect on bone and muscle. However, whether it can prevent post-menopausal osteoporosis is not clear.

Vitamin K: serum concentration of vitamin-K especially K2 moieties fall as a person gets older and is decreased in patients with hip fractures. Treatment with menatetrenone, a vitamin-k compound has been associated with increase in BMD and is approved in Japan. A positive effect on fragility fractures is suggested by a small controlled study.

Thiazide diuretics: Reduce the tubular reabsorption of calcium and could decrease bone turnover and bone loss, but their role in management of osteoporosis have not been established.

Fluoride: It is incorporated into the hydroxyapatite component of bone and stimulates osteoblast recruitment and activity. In humans sodium fluoride increases spine BMD linearly with time, with little effect at hip. The findings of two large placebo controlled studies indicate that it does not decrease the incidence of vertebral fractures.

Ipriflavone: It is a synthetic compound that belongs to the family of isoflavones. Although preliminary reports suggested that it could prevent bone loss, it does not seem to reduce the incidence of fractures in osteoporotic women.

Statins: increase bone mass and strength in rats but their effectiveness in prevention of fractures is still not proved.

C. Non-Pharmacological Measures

Diet: The nutrients known with certainty to be important are calcium, vitamin D and Protein. Other nutrients that may be important are phosphorus, zinc, vitamin C and K, manganese and copper. The 1994 consensus development conference on optimum calcium intake recommended 1200 – 1500 mg daily for adolescents, 1000 mg daily for adults up to age 65 years, and 1500 mg daily for postmenopausal women not receiving estrogen and for elderly people. The National Osteoporosis Foundation, USA, recommends 1,200 mg/d for post-menopausal women.

Exercise: has a wide variety of beneficial health effects. However, exercise does not bring about substantial increases in bone density. Regular exercise early in life leads to high peak bone mass and in later life delays physiologic decrease in BMD with age. Research has not yet determined what type of exercise is best for osteoporosis or for how long. Until research has answered these questions, weight-bearing and muscle strengthening exercises, such as walking, are recommended. Walking, weight bearing and high impact exercises increase BMD by 1-2 % but the benefit is not sustained once the exercise programme is stopped. The benefit of exercise for osteoporosis has mostly to do with decreasing the risk of falls, probably because balance and mobility is improved and / or muscle strength is increased.

Results of controlled studies have shown that exercise can increase muscle mass and strength and reduce the risk of falls by about 25% in frail elderly individuals. However no controlled study has shown that such exercise programmes can reduce the risk of fracture, irrespective of age. Specific interventions aimed at preventing falls and their consequences in the elderly need to be developed. It is important to avoid exercises that can injure already weakened bones. Marathon running in young women that leads to weight loss and loss of menstrual periods can actually cause osteoporosis.

Fall Prevention: Hip protectors should be recommended to those prone to falls. Benzodiazepines, hypnotics, antidepressants and medications causing hypotension should be reduced as they increase chances of fall. Slippery floor should be avoided and adequate lighting should be installed. Visual impairment e.g., cataract should be detected and treated.

Smoking: one pack of cigarettes per day throughout adult life can itself lead to loss of 5% to 10% of bone mass. Smoking cigarettes decreases estrogen levels and can lead to bone loss in women before menopause. Smoking cigarettes can also lead to earlier menopause. In postmenopausal women, smoking is linked with increased risk of osteoporosis.

Alcohol and caffeine: data on the effect of regular consumption on osteoporosis is not as clear as with exercise and cigarettes. In fact, research regarding alcohol and caffeine as risk factors for osteoporosis shows widely varying results, and is controversial. Certainly, these effects are not as powerful as other factors. Nevertheless, moderation of both alcohol and caffeine is prudent.

D. Treatment of the underlying cause: In cases of secondary osteoporosis it is important to treat the underlying cause such as hyperparathyroidism, Vitamin D deficiency, malabsorption syndrome, prolonged treatment with corticosteroids and anticonvulsants.

MONITORING OF OSTEOPOOROSIS TREATMENT

Approximately 10 -15% of patients with osteoporosis fail to respond to treatment. As in most chronic diseases, compliance is usually poor in patients on long term treatment of osteoporosis. Thus, the aim of monitoring should be to increase adherence to treatment as well as to ascertain response to treatment. Because fracture events are uncommon, they cannot be used to monitor drug effectiveness. Repeat BMD measurement especially at the spine, is recommended once every 2 years to confirm treatment response.
Monitoring osteoporosis treatment using DXA scans is highly controversial. Recent scientific evidence questions the usefulness of such interval monitoring. Reasons why repeating bone density scans is extremely tricky include:

1. Bone density changes so slowly that the changes may be smaller than the measurement error of the machine. In other words, repeat DXA scans cannot distinguish between a “real” increase in bone density and a mere variation in measurement from the machine itself. Typically, BMD changes 1% per year, which is less than the error of a DXA machine (usually in the range of 3%). Changes of less than 2 to 4% in the vertebral and 3 to 6% at the hip from test to test can be due to the precision error of the method.

2. Whereas the real purpose of prescribing osteoporosis treatment is to decrease future bone fractures, there is no good correlation between increases in bone density as measured by DXA with decreases in fracture risks with treatment. There are multiple examples of this in recent clinical studies. For example, the improvement in BMD only accounted for 4% of the reduction in spine fracture risk with raloxifene, 16% of the reduction in spine fracture risk with alendronate, and 18% of the reduction in spine fracture risk with risendronate. Thus, improvement in BMD does not indicate the amount of the anti-fracture benefit of osteoporosis medication. Prescribing medication may decrease a person’s risk of fracture even when there is no apparent increase in BMD. Physicians and non-physicians alike are often surprised to learn this information.

3. Even if the DXA scan shows continued deterioration in bone density during treatment, no research data exists demonstrating that changing a medication, combining medications, or doubling medication doses will be safe and helpful in decreasing the future risk of fractures compared to just continuing the same medication.

4. Even if a person’s bone density deteriorates during treatment, it is quite likely that the person would have lost even more bone density without treatment.

5. Recent research has shown that women who lose bone density after the first year of menopausal hormone therapy will gain bone density in the next two years, whereas women who gain in the first year will tend to lose density in the next two years of therapy. Therefore, bone density during treatment naturally fluctuates and may not be indicative of the fracture protection of the medication.

Use of biochemical markers of bone formation and resorption has been proposed as a good way to monitor antiresorptive treatment. The markers usually used are type I collagen N-terminal telopeptide (NTX) in urine and type I collagen C-telopeptide (CTX), deoxypyridonoline and tartrate resistant acid phosphatase (TRAP) in blood. Serum or urinary osteocalcin and bone specific alkaline phosphatase are also used. Findings of several studies have shown a significant inverse correlation between the short term fall in bone turnover markers and the 2-3 year rise in BMD at various skeletal sites with HRT and bisphosphonates. Cut-off values for these decreases, for a specific marker and the treatment that will identify responders and non-responders with adequate sensitivity and specificity have been proposed by the committee of scientific advisors of the International Osteoporosis Foundation. Maximum suppression in the order of 50% is seen within three months of starting therapy. Females with high levels of bone remodeling markers at baseline may respond better to treatment. This would allow earlier identification of non-responders. They exhibit diurnal and day to day variation and are influenced by many other factors. Moreover, there is problem of cost and availability. In view of these difficulties it is currently recommended that the use of bone turnover markers should be confined to specialist centers and research studies. Whether BMD measurements or bone turnover markers, or both, are used to monitor treatment response, there remains no proof that such an approach improves long term compliance to treatment.

REFERENCES


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