

# Current Therapy of Osteoporosis

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**Abstract:** Osteoporosis is a systemic skeletal disease that is characterized by low bone mass with a consequent increase in bone fragility and susceptibility to fracture. Most common causes of osteoporosis include postmenopausal state in females and senility in males. It can also be secondary to a number of systemic diseases or chronic drug therapy. Treatment modalities include lifestyle modifications like performing regular exercises, cessation of smoking and alcohol intake, and consumption of food items rich in calcium and vitamin D. The drug therapy includes calcium and vitamin D supplementation, hormone replacement therapy, bisphosphonates, selective estrogen receptor modulators e.g. raloxifene, and calcitonin. Other investigational agents include phytoestrogens, tibolone, fluoride, growth hormone, anabolic steroids and thiazide diuretics.

**Key words :** *Osteoporosis, Hormone Replacement Therapy, Bisphosphonates, Selective estrogen receptor modulators.*

## Introduction

Osteoporosis is primarily a geriatric disorder and is relatively new to medicine. Some bone loss with increasing age is normal in both men and women. Once peak bone mass has been attained, usually between the ages of 20 and 30 years, women and men lose bone at a rate of about 0.5 to 1 percent yearly, although this varies considerably from person to person. Over the past 2 decades the definition of osteoporosis has changed due to advances in the knowledge of its pathophysiology as well as technical advances in quantifying and interpreting bone mass<sup>1</sup>. The world health organisation (WHO) has defined osteoporosis on the basis of bone mass represented by a T score that normalises bone mass relative to mean bone mass of younger adults<sup>2</sup>. Indians are known to suffer from osteoporotic fractures a decade earlier than the western counterparts. Out of 6.1 crore osteoporotic patients, it is estimated that 50 lac will have fractures of spine or hip every year<sup>3</sup>.

Dual Energy X-ray Absorptiometry (DEXA) and Bone Mineral Density (BMD) are considered the best methods for assessing risk of osteoporotic fracture and for confirming the diagnosis of osteoporosis. Causes of osteoporosis may be classified as primary and secondary.

**Primary :** Postmenopausal (Type 1 Osteoporosis); Senile (Type 2 Osteoporosis); Senile (Type 2 Osteoporosis); Idiopathic.

**Secondary :** Cushing's Syndrome (including Glucocorticoid Therapy), Hyperthyroidism; Hypogonadism in men; Immobilization; Chronic heparin administration; Osteogenesis Imperfecta; primary Hyperparathyroidism; Osteomalacia; Myeloma; Mastocytosis; Renal Osteodystrophy.

## Treatment modalities

**Lifestyle modifications<sup>4</sup> :** Certain lifestyle changes should be incorporated in the daily routine like performing aerobic, weight bearing or isometric exercises on a regular basis. Walking also helps in maintaining bone mass. Outdoor exercises may increase exposure to sun and thus induce vitamin D synthesis in skin. All elderly individuals should be encouraged to stop smoking and decrease alcohol intake and should undergo regular clinical and therapeutic drug monitoring for agents that are known to enhance bone loss on chronic use (anticonvulsants like phenytoin, heparin,

glucocorticoids, lithium therapy), that can alter calcium absorption (tetracycline, loop diuretics) and for other agents like sedatives, anxiolytics, antidepressants, phenothiazines and vasodilators, that are known to increase the frequency of falls.

**Calcium and Vitamin D Therapy :** Low calcium intake is associated with accelerated bone loss; calcium supplementation alone has been shown to decrease occurrence of new vertebral fractures in women who have already had such fractures. The current recommended daily calcium intake is 1200-1500 mg per day in postmenopausal women. Calcium supplementation alone or in combination with hormone replacement therapy also appears to retard bone loss from the femoral neck in early postmenopausal women<sup>5,6</sup>. The National Research Council Institute of Medicine recommends Vitamin D 400 IU/day for those in the age group of 51-70 years and 600 IU/day for those who are above 70 years<sup>7</sup>.

**Hormone Replacement Therapy :** The role of HRT in the prevention of osteoporosis is controversial<sup>8</sup>. The ability of estrogen to prevent the rapid bone loss associated with menopause is well accepted. Most of the available observational data on HRT show an association between estrogen use and reduction of fracture risk<sup>9</sup>. The main goal of HRT (oestrogen or oestrogen and progesterone combination) is to alleviate the symptoms of menopause. HRT can be administered orally, transdermally, topically, intranasally; or as subcutaneous implants. It reduces serum and urinary markers of bone turnover, which return to premenopausal values. Doses of 0.625mg conjugated estrogens or 1-2mg 17 beta estradiol have been found to be effective with only less than 10% of women continuing to show bone loss. Fracture data from the HERS study have recently been analyzed in an effort to provide additional clinical information on the effect of HRT on reducing bone fractures<sup>10</sup>. HERS was a large randomized study designed to evaluate the effect of HRT on cardiovascular risk; fracture data were collected as a secondary outcome<sup>11</sup>. Unfortunately, the results of this study did not definitively address the role of HRT in fracture reduction in patients with osteoporosis. Recently, a meta-analysis of randomized trials of HRT was performed, including those studies in which patients were treated for at least 12 months, and data were collected on the occurrence of nonvertebral fractures<sup>12</sup>. The most significant conclusion of this meta-analysis is that the effect of HRT on fracture risk diminishes among women initiating HRT after the age of 60.

It can thus be concluded that the evidence regarding the efficacy

of post-menopausal estrogen for the prevention of osteoporotic fractures is weak. However, it should be noted that the results of the HERS study and the above meta-analysis do not exclude an anti-fracture benefit of HRT; the weakness of the evidence may reflect the lack of randomized controlled trials specifically focusing on fracture endpoints, not the lack of efficacy of HRT itself.

**Bisphosphonates** : Bisphosphonates are analogues of pyrophosphates, which have potent inhibitory effects on bone resorption. These drugs are effective drugs in bone disorders characterized by increased bone resorption, such as paget's disease, osteoporosis, hypercalcaemia of cancer, multiple myeloma, and bony metastasis. Candidates for bisphosphonate treatment include those postmenopausal women at increased risk of osteoporosis who forego HRT, men with osteoporosis, and all individuals receiving high-dose corticosteroid therapy<sup>13</sup>. Bisphosphonates are characterized by poor intestinal absorption, which is further reduced if the drug is given with calcium or iron. These agents are therefore never given at meal times or with dairy products. They should be taken with a full glass of plain water in the morning at least half to one hour before breakfast, as their oral bioavailability is extremely low 10%<sup>14</sup>. The first randomized controlled trial of bisphosphonates in postmenopausal osteoporosis used cyclical etidronate (400mg/day for two weeks, then repeated every three months). Alendronate and risedronate have recently been approved for prevention and treatment of postmenopausal, glucocorticoid-induced, and male osteoporosis<sup>15</sup>. For patients who are intolerant to oral bisphosphonate, pamidronate is the only intravenous bisphosphonate that is currently available. Bisphosphonates can cause gastrointestinal upset; oesophagitis and oesophageal ulceration can be very distressing. These agents can also cause electrolyte imbalance, therefore should be used caution if renal function is impaired<sup>16</sup>.

**Selective Estrogen Receptor Modulators (SERMS)** : Tamoxifen, raloxifene and droloxifene are Selective Estrogen Receptor Modulators (SERMS) having differential estrogen agonistic and antagonistic activities on different tissues. It has recently been approved by FDA for prevention of osteoporosis in a dose of 60mg/day. Raloxifene causes an increase in bone mineral density (BMD) at the lumbar spine, total hip, and femoral neck, but the effect seems to be less than that of estrogen or alendronate. Raloxifene and tamoxifen spare anti-resorptive effects of estrogen on bone<sup>17</sup>. Recent data from the multiple outcomes of raloxifene evaluations showed that 60 and 120mg daily doses of raloxifene significantly decreased vertebral fracture risk during the first 36 months of treatment, compared with placebo. The most common adverse effects of raloxifene are hot flashes and leg cramps. The only serious adverse events reported with raloxifene treatment were venous thromboembolic episodes, which included deep venous thrombosis and pulmonary embolism<sup>18</sup>.

**Calcitonin** : This peptide, which is normally produced by the C cells of the thyroid gland, inhibits actions of osteoclasts and decreases bone resorption. Subcutaneous or intranasal calcitonin is approved for the treatment of postmenopausal osteoporosis the effect is predominantly on lumbar spine, but is small (1-3% increases in BMD), with little effect on cortical bones<sup>19</sup>. The dosage of calcitonin is 2200 IU/day intranasally or 100 IU/day subcutaneously<sup>20</sup>. It should be taken with calcium and vitamin-D, whenever required. Adverse effects with intranasal administration include transient rhinorrhoea, nasal discharge, and nasal stuffiness. Diarrhoea, nausea, vomiting, loss of appetite, stomach pain, flushing, irritation at the injection site, and increased urinary frequency may occur with subcutaneous administration.

## **Investigational anti-resorptive agents and bone formation agents :**

**Phytoestrogens** : like isoflavones and lignans are plant substances that have some estrogenic effects, but are generally weaker agents. Isoflavones (genistein, daidzein) come from metabolised soybean and soy products. Lignans (enterodiol, enterolactone) are metabolised from precursors in flax seed, cereals, vegetables, fruits, and legumes. Animal data support possible decrease in bone loss with phytoestrogens<sup>21</sup>. There is evidence that flavonoids may play a role in preventing osteoporosis. Treatment with ipriflavone, an isoflavone derivative, for a period of one year has been shown to reduce pain and morbidity in 73% of the patients with osteoporosis. Many clinical trials are ongoing and results are awaited.

**Fluoride** : Sodium fluoride increases bone volume, an effect due specifically to increased osteoblastic activity. In doses of 30 to 60mg/day, fluoride increases trabecular bone mass in many but not all patients. The sustained-release product maintains lower and therapeutic fluoride levels (15-190ng/ml). On supplementation, fluoride becomes a part of bone and increases its crystallinity, thereby decreasing resorption. Bone thickness is also increased by stimulating osteoblasts, but new bone does not bridge current bone to increase lattice and strength. Role of Intermittent fluoride regimens in osteoporosis is under investigation<sup>22,23,24</sup>.

**Hormones** : Agents such as parathormone, growth hormone, and anabolic steroids are being investigated for enhancing bone formation but generally limited by adverse reactions like glucose intolerance, hyperinsulinemia, hypertension, and edema or lower efficacy<sup>25</sup>.

**Thiazides** : Thiazides and other calcium retaining diuretics have shown a beneficial effect on bone density in postmenopausal women. These reduce calcium excretion through increased calcium reabsorption in the distal tubule. However, these diuretics are not without risk and may aggravate hypokalemia in corticosteroid treated patients<sup>26</sup>.

**Miscellaneous** : Oral strontium, trace elements such as copper, magnesium and zinc, non steroidal anti-inflammatory agents, proton pump inhibitors, potassium bicarbonate, ephedrine, amylase, and vitamin K are all being evaluated as potential treatment modalities for osteoporosis<sup>27</sup>. Recently, the role of melatonin has also been reported in bone remodeling. Melatonin, through its free radical scavenging and antioxidant properties may impair osteoclast activity and bone resorption. Melatonin, which has shown potential in some studies as a novel mode of therapy for augmenting bone mass deserves to be studied<sup>28</sup>.

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### ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH

The need for uniform ethical guidelines for research on human subjects is universally recognised. It has acquired a new sense of urgency as the critical issues in the area of biogenetic research involving human subjects have become acute. Apart from the mandatory *clinical trails* on new drugs, a number of *diagnostic procedures, therapeutic interventions and prevention measures* including the use of vaccines, are being introduced which involve human subjects. Further the advent of *new medical devices and radio-active materials* and therapeutic benefits of *recombinant DNA products* have added a new dimension to the ethical issues that need to be considered before evaluating these for their efficacy, utility and safety.

Any research using the human beings as subjects shall bear in

mind the following principles of : i) **essentiality**, (ii) **voluntariness**, **informed consent**, (iii) **non exploitation**, (iv) **privacy and confidentiality**, (v) **precaution and risk minimisation**, (vi) **professional competence**, (vii) **accountability & transparency**, (viii) **maximisation of public interest and distributive justice** (ix) **institutional arrangements** (x) **public domain** (xi) **totality of responsibility** and (xii) **compliance**.

Recent advances in the field of **Assisted Reproductive technologies, organ transplantation, Human genome analysis, and gene therapy** promise unquestionable benefits to mankind. At the same time, they raise many questions of law and ethics, stimulating public interest and concern.

(Source : ICMR Publication 2000)

### Drug Profile

#### SIROLIMUS

Sirolimus is a carbocyclic lactone-lactam macrolide-antibiotic prepared through natural fermentation from the soil actinomycete streptomyces hygroscopicus. sirolimus first demonstrated antifungal activity but, due to its structural similarity to tacrolimus, it was used for its immunosuppressive activity.

**Mechanism of action** : Sirolimus inhibits T. Lymphocyte activation and proliferation that occurs in response to antigenic and cytokine stimulation by a mechanism that is distinct from that of other immunosuppressants. Sirolimus also inhibits antibody production. In cells, it binds to the immunophilin, FK binding protein-12 (FKBP-12), to generate an immuno-suppressive complex. The sirolimus; FKBP-12 complex has no effect on calcineurin activity. This complex binds to and inhibits the activation of the mammalian target of Rapamycin (MTOR) a key regulatory kinase. This inhibition suppresses cytokine-driven T cell proliferation, inhibiting the progression from the G1 to the S-phase of the cell cycle.

**Pharmacokinetics** : It is readily but poorly absorbed after oral administration with an estimated bioavailability of 15%. Once absorbed into systemic circulation, it easily enters cells because of its high lipophilicity. 95% of drug is bound to RBG, 3% is found in plasma and 1% in lymphocytes and granulocytes. It is 100 times more potent than cyclosporine probably because of increased binding to RBG and decreased binding to lymphocytes.

**Metabolism & excretion** : It undergoes extensive metabolism by the CYP 3A4 system both in liver and small intestine. It is also a substrate of the efflux pump, P-glycoprotein, which is also found in the intestinal wall. The terminal half life (t<sub>1/2</sub>) of drug is long ranging from 57 to 62 hours suggesting that once - daily dosing is adequate. Over 90% of the drug is removed through the faeces, and only a minor amount (2.2%) is excreted in urine. No dosage adjustment is necessary in patients with renal dysfunction. It is not removed by dialysis. It is extensively metabolized in the liver; therefore dosage modification is necessary in patients with hepatic dysfunction; 1/3rd of the

recommended dose should be given to patients with mild to moderate hepatic dysfunction. Sirolimus is metabolized by the CYP3A4 enzyme system. Any agent that alters the concentration of cyclosporine is expected to alter sirolimus concentrations. these include both enzyme inducers (eg rifampin, phenytoin) and inhibitors (azoles-antifungal, erythromycin, diltzem)

**Indication** : It is Indicated for the prophylaxis of organ transplant rejection. It is recommended that sirolimus should be used initially in a regimen with cyclosporine and corticosteroids.

**Dosage & Administration**: It is to be given orally once a day. The initial dose of sirolimus should be administered as soon as possible after transplantation. A daily maintenance dose of 2 mg is recommended for use in renal transplant patients with a loading dose of 6mg. It should be taken consistently with or without food. It must be taken 4 hours before/after cyclosporine dose.

**Adverse Effects** : The commonly reported adverse effects include abdominal pain, asthma, back pain, chest pain, fever, headache CVS hypertension; *digestive* Constipation, Diarrhoea, dyspepsia, nausea, vomiting; *metabolic and nutritional* : increased creatinine, oedema, hypercholesterolemia, hyperkalemia hyperlipidemia, hypokalemia, Wt gain, peripheral oedema; *musculo skeletal* - arthralgias; *nervous system* - tremor, insomnia; *respiratory system* - dyspnoea, pharyngitis, URI; *hematological* - Anaemia, leukopenia, thrombocytopenia

**Drug Interaction**: Drugs that may increase sirolimus blood concentration include: *calcium channel blockers* - nifedipine, verapamil; *antifungal* - clotrimazole, fluconazole, itraconazole; *macrolide antibiotic* - clarithromycin, erythromycin; *prokinetic agents* - cisapride metoclopramide;

Drugs that may decrease sirolimus concentration include *anticonvulsants* carbamazepine, phenobarbitone, phenytoin; *antibiotics* - rifabutin, rifapentine; *vaccinations* - vaccination may be effective during Sirolimus therapy.

Compiled by Dr. Pradeep Chatterjee