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Review Article

Advances in Non-Pharmacological and Pharmacological Management of Osteoporosis

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Abstract

Osteoporosis is a skeletal disorder characterized by decrease in bone mass and micro- architectural alterations. It is a major public health concern because a bulk of bone mineral is lost even before the symptoms develop. Delay in diagnosis, lifelong treatment and complications, like disability; affect the quality of life. The availability of advanced techniques, for measuring bone mineral density, help in diagnosis and assessing fracture risk. New treatments with lifestyle interventions have been shown to reduce the risk of fractures at vulnerable sites. Two types of drugs are available for the treatment of osteoporosis, drugs inhibiting bone resorption and drugs stimulating bone formation. Inspite of all these management options, there is a need to discover new agents to reduce osteoporotic fractures for the better quality of life in these patients.

Keywords: Bone Mineral density; Anti-resorptive agents; Bone formation; Quality of life

Introduction

In most of the developed and developing countries, increasing trend towards the ageing population is observed due to increased life expectancy. Advancement in the age increases the problems associated with it. Activities of Daily Living (ADL) get affected because of ageing and age related conditions like osteoporosis, osteoarthritis, etc. Once ADL affected dependency increases and vice a versa, it leads to progression of disability. Osteoporosis is the common problem occurring in ageing population. It is an important public health issue because of the high rate of fractures associated with it. According to Marwaha et al, high prevalence of osteoporosis was observed in elderly Indian subjects [1]. Even fractures without injury are common [2]. 50% women and 36% of men over 50 years of age were noted to have low bone mass [3]. It affects 8. 5% of otherwise healthy males aged 50 years and above [4]. Osteoporosis is responsible for millions of fractures annually, mostly involving the lumbar vertebrae, hip, and wrist. Osteoporotic fractures also increase economic burden on health-care systems worldwide.

Osteoporosis

Osteoporosis is a skeletal disease characterized by low bone mass and micro architectural deterioration with a resulting increase in bone fragility and hence, susceptibility to fractures [5]. According to WHO, it is defined as-"A bone density that falls 2.5 Standard Deviation (SD) below the mean for young healthy adults of the same gender T-score of 2.5". Low bone density- postmenopausal women who fall at the lower end of the young normal range of T-score [6].

Types of Osteoporosis

The commonest types of osteoporosis are postmenopausal (Type 1) and Senile (Type 2).

Osteoporosis may also occur as an adverse effect of long term administration of glucocorticoids, as a manifestation of thyrotoxicosis or hyperparathyroidism, as a feature of Malabsorption or as a consequence of alcohol abuse and cigarette smoking.

Risk factors [7]

1. Age- Advancing age shows higher risk of fractures of femoral neck bone because of low Bone Mineral Density (BMD), quadriceps weakness and higher body sway.
2. Gender- Females are more prone for fractures, especially menopausal women, due to loss of their estrogenic support.
3. Race- White or Asian race show higher incidence of fractures.
4. Body weight - Low body weight as well as high body weight contributes to fractures.
5. Family history- Family history of osteoporotic fractures is said to be an important risk factor due to low bone calcium stores.
6. Life style- Sedentary lifestyle, excessive alcohol (> 2 drinks per day), caffeine, and tobacco, low calcium and/or vitamin D intake &inadequate sun exposure are also associated with risk of osteoporosis.
7. Drugs- Glucocorticoids, Thyroid over replacement, Anticonvulsants (phenytoin, phenobarbital), Lithium, Heparin (long-term), drugs producing hypogonadism (aromatase inhibitors, antimetabolite chemotherapy, medroxyprogestrone, gonadotropin-releasing hormone agonists),Pioglitazone,Proton pump inhibitors, etc are known to be contributors of osteoporosis.
8. Endocrine Disorders- Cushings' syndrome, Hyperparathyroidism, Hypogonadism and Hyperthyroidism are associated with osteoporosis.

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Estimation of bone mass

Bone Mineral Density (BMD) is the amount of mineral matter per square unit area of bone. Bone mass is best estimated by bone densitometry which measures (BMD). It is expressed in terms of T-Score & Z- Score and Dual-energy X-ray Absorptiometry (DXA) is the important tool for the diagnosis of osteoporosis and a gold standard imaging technique since it has predictive value [8,9]. T-Score is the BMD at the bone site when compared to the young normal reference mean. Z-score is the comparison to the age-matched normal and is usually used in cases of severe osteoporosis. Negative scores indicate lower bone density, and positive scores indicate higher BMD [10].

Normal bone density=Tscore-1 to +1, Osteopenia= T score -1 to -2.5.

T score -1 to -2 requires only general health measures such as dietary advice, physical exercise, Calcium & Vitamin D supplementation, etc. T score from -2 to -2.5 requires anti-resorptive drug treatment in the presence of one or more risk factors for osteoporosis. The risk of fracture increases 1.5-3 times each standard deviation of BMD below the reference population. Early identification and management of osteopenic patients will help reduce the morbidity as well as economic burden.

Bone homeostasis

At the cellular level, bone is made up of three types of specialized bone cells: Osteoblasts, Osteocytes and Osteoclasts [11].

Bone remodeling

Consists of a sequence of events involving the dynamic interaction of osteoclasts (bone-resorbing cells) and osteoblasts (bone-forming cells) (Figure 1).

The entire remodeling process takes about 100 days on an average. During this process, some of the osteoblasts remain inside the bone tissue and are converted to osteocytes. Once the new bone has been mineralized, the remodeling process is complete.

Bone remodeling continues throughout adulthood, with each remodeling process lasting 6-49 months. The balance between bone resorption and bone formation is usually maintained until the third or fourth decade of life [12]. Hormonal and nutritional deficiencies as well as age-related imbalance favor resorption over bone formation resulting into osteoporosis.

Approach for management of osteoporosis

The four major goals in the treatment of osteoporosis are:

- To prevent fractures
- To stabilize bone mass or achieve increased bone mass
- To relieve symptoms of fractures and skeletal deformity
- To maximize physical function

Non pharmacological management of osteoporosis

A comprehensive approach is required for the treatment of osteoporosis.

Both pharmacologic and non-pharmacologic approaches for treatment need to be considered.

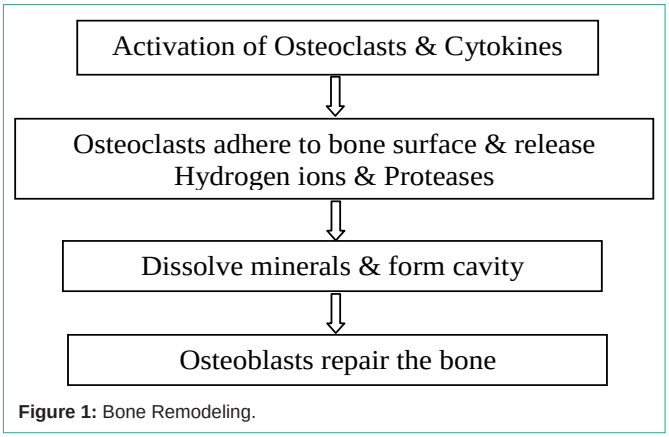

Figure 1: Bone Remodeling.

1. Lifestyle modification can help in prevention of osteoporosis:

- Reduce alcohol consumption [13].
- Reduce caffeine consumption. Caffeine may interfere with calcium absorption.
- Quit smoking- the risk for osteoporosis diminishes after quitting smoking [14].

2. **Exercise:** In post menopausal women, it has been seen that weight-bearing exercise helps to prevent bone loss [15]. Exercise also has beneficial effects on neuromuscular function and it improves co-ordination, balance, and strength, thereby reducing the risk of falling.

Walking is a practical way to start. Swimming or water exercises also benefit by improving muscle strength. A combined exercise program (resistance + aerobic + impact) is recommended for an enhancement of spine BMD [16]. Exercise should be consistent, optimally at least three times a week.

3. Restoration of Calcium and vitamin D which are critical elements in bone homeostasis:

Calcium

The preferred source of calcium is dairy products. Dietary modification for calcium- Calcium rich food & exposure to sunlight is essential as a non-pharmacological approach to osteoporosis. Calcium supplements if needed, should be taken in doses <600 mg at a time, best taken with food as an adjuvant to other therapies. It reduces bone loss and suppresses bone turnover. The only adverse effects associated with calcium supplements are mild GI upset and constipation (mostly with carbonate salts).

Vitamin D

Presently, Vitamin D deficiency has been recognized as an epidemic [17]. Vitamin D is converted to its most active form, calcitriol, by hydroxylation in the liver and kidneys as follows (Figure 2).

Active form of Vitamin D, Calcitriol increases plasma Ca^{2+} by mobilizing it from bone, increasing its absorption in the intestine and decreasing its excretion as well as increasing reabsorption by the kidney. Parathyroid hormone (PTH) increases blood Ca^{2+} by increasing calcitriol synthesis, mobilising Ca^{2+} from bone and reducing renal Ca^{2+} excretion. Paradoxically, small doses of PTH given

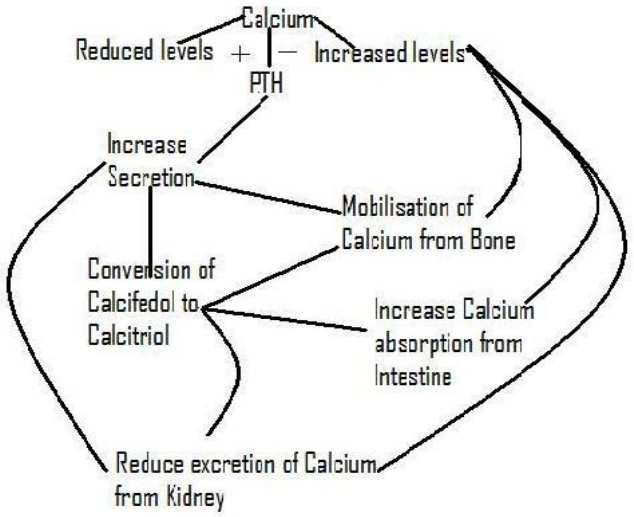

Figure 2: Active form of Vitamin D.

intermittently increase bone formation through an anabolic effect. It promotes the recruitment of osteoclast precursor cells to resorption site and differentiation of osteoclasts. In osteoblasts, calcitriol induces production of several proteins, including osteocalcin, a vitamin K-dependent protein that contains g-carboxy glutamic acid residues, and Interleukin-1 (IL-1), a lymphokine that promotes bone resorption & calcification of matrix.

4. Fall prevention requires environmental modifications [18]:

In advanced age,in postmenopausal women& in individuals with low BMD some movements should be avoided like lifting heavy weights or lifting weight in forward bending position. Also pectoral stretching, deep breathing, back extension exercises& kyphotic posturing should be performed cautiously if needed.

5. Back braces and hip protectors, can help in the prevention and treatment of fractures.

6. Kyphoplasty is a minimally invasive procedure performed on spine in appropriately selected patients which improves pain and reduces occurrence of new vertebral fractures [19].

Pharmacological management

Currently used drugs for treatment of osteoporosis are:

1. Calcium & Vitamin D-

e.g. Calcium carbonate • Calcium citrate • Cholecalciferol

2. Antiresorptive drugs-that decrease bone loss.

e.g. Bisphosphonates, Calcitonin, Selective Estrogen Receptor Modulators (SERMs).

3. Anabolic agents-that increase bone formation.

e.g. PTH, Teriparatide, Cinacalcet, Fluoride.

4**. RANKL Antibody**-Denosumab.

5. **Other Agents**- Strontium ranelate, Sodium fluoride.

Management of the Underlying Disease with Drugs

Antiresorptive drugs

A. Bisphosphonates

Bisphosphonates haveappeared as the most effective & promising agents in the past decade. Daily Alendronate and Risedronate have reduced the risk of single and multiple spine fractures in women with low bone mineral density [20].

First generation - e.g. Etidronate, Tiludronate:

- Act by promoting apoptosis of osteoclasts.

- Less potent.

Second generation – e.g. Alendronate, Pamidronate, Ibandronate:

- 10-100 times more potent.

Third generation- e.g. Risedronate, Zolendronate:

- 10,000 times more potent.

Second & Third generation compounds are with N-containing side chains which prevent osteoclast action by inhibiting prenylation reactions required for membrane anchoring of functional proteins. They also interfere with metabolic mevalonate pathway and osteoclast function [21].

Bisphosphonates have a strong affinity for bone apatite. They are potent inhibitors of bone resorption and produce their effect by reducing the recruitment and activity of osteoclasts and increasing their apoptosis.

Strong affinity for calcium phosphate
↓
Concentrate in mineralized tissue
↓
Disrupt cytoskeleton and ruffled border of osteoclasts
↓
Acids secreted by osteoclast dissociates it from mineral
↓
Within osteoclast, blocks mevalonate pathway
↓
Osteoclast apoptosis

Uses-Alendronate, Risedronate, and Ibandronateare usedforprevention and treatment of postmenopausal osteoporosis while Risedronate and Alendronate for steroid-induced osteoporosis. Alendronate and Risedronate are alsopreferred for osteoporosis in men.

Adverse effects associated with these drugs are - Nausea, headache, abdominal pain, diarrhoea, occasionally may cause oesophagitis and oesophageal ulcer. Gastritis can be minimized by taking the drug on empty stomach in early morning with a glass full of water and patient is instructed not to lie down or take food for at least 30 min. They can also cause fever, joint pain, myalgia and ocular inflammation. Zolendronate is found to benephrotoxic. Higher doses of bisphosphonates can cause osteonecrosis of the jaw.

B. Hormones

1. **Calcitonin**- It is approved for the treatment of postmenopausal

osteoporosis and bone resorption. It increases bone mass mainly in the spine. Intra nasal salmon calcitonin- 200 IU daily is more effective in preventing lamellar bone loss than cortical bone mass but it does not appear to be as effective as bisphosphonates. PROOF study (Prevent Recurrence of Osteoporotic Fracture) has proved that Salmon calcitonin nasal spray significantly reduces the risk of new vertebral fractures in postmenopausal women with osteoporosis [22].

2**. Teriparatide**- The recombinant form of PTH 1-34 is approved for the treatment of osteoporosis. It stimulates bone remodeling by inducing an increase in bone formation followed by a slower increase in bone resorption [23]. A dosage of 20 mcg subcutaneously daily increases BMD bone mass & bone strength by stimulating periosteal and endosteal bone formation. It is the first drug available with anabolic action on the bone. Teriparatide is approved for use for only 2 years for patients of osteoporosis. Trials examining the sequential use of teriparatide followed by a bisphosphonate after 1 or 2 years are in progress and look promising [24].

3. **Estrogen**-The majority of estrogen effects on bone resorption are mediated indirectly through paracrine factors produced by osteoblasts. They act by increasing IGF-1 and TGF- β & suppressing IL-1 (α and β), IL-6, TNF-, and osteocalcin synthesis.

Estrogen was used previously for treatment of post menopausal osteoporosis, however the concerns associated with its use i. e. development of breast cancer, endometrial carcinoma and failure to reduce the development of heart disease, have reduced enthusiasm for this form of therapy.

4. **SERM**- It prevents the risk of breast and uterine carcinoma associatedwith estrogen use while maintaining the benefit of estrogen to the bone.

Raloxifene - It causes dose dependent increase in osteoblastic activity and in osteoclastic activity. It protects against spine fractures but not against hip fracture unlike bisphosphate and teriparatide which protect against both [25].

It is used in the dose of 60 mg once daily for the prophylaxis of menopausal osteoporosis.

Adverse effects associated with this drug are - hot flushes, leg cramps & thromboembolic disease.

Hormone Replacement Therapy is preferred in early menopause symptoms while SERM is preferred in middle and late menopause.

Recent Advances

Strontium ranelate

Strontium ranelate is another treatment option for the prevention of osteoporosis. Strontium is laid down on the surface of newly formed bone where it decreases osteoclastic activity and reduces bone resorption [26]. Simultaneous administration of calcium and phosphatesis required for bone mineralization. At the same time, strontium induces the differentiation of pre-osteoblasts to osteoblasts and increases markers of bone formation. Overall, strontium increases bone mass and strength [27]. It has not been approved yet but clinical trials have found that strontium ranelate reduced the risk of new vertebral fractures by about 25% and non-vertebral fractures by 15%. Strontium may cause minor gastrointestinal problems but does not appear to have any serious adverse effects.

Denosumab

Denosumab is a human monoclonal antibody to RANKL (Receptor for activation of nuclear factor k ligand) that suppresses bone resorption by interfering with RANKL/RANK induction of osteoclast differentiation and function. Inactivation of the RANKL → RANK → NF-κB pathway by Denosumab inhibits gene expression required for osteoclast function and decreases bone resorption in both cortical and trabecular bone. The increase in BMD is higher than that obtained with the more potent bisphosphonates. Denosumab has produced reduction in the risk of vertebral, non vertebral and hip fractures in women with osteoporosis [28].

Romosozumab

Humanized monoclonal antibody

↓

Inhibits sclerosin

↓

Immediate increase in bone formation markers

↓

Moderate sustained reduction in bone resorption markers

Since, sclerosin genes are expressed only in skeletal tissue, it produces less adverse effects. There is no data on anti-fracture efficacy and long term safety of this drug. Currently it is in phase 3 trials and is administered by subcutaneous injection at monthly or 3 monthly intervals.

Osteoprotegerin (OPG)

Osteoblasts synthesise and release a molecule osteoprotegenin which inhibits RANKL binding to RANK. So, in near future, OPG analogue or agonist could be the potential the rapeutic agent for osteoporosis [29].

Thiazide diuretics

These decrease calcium excretion and are useful in preventing renal stones. They may also be useful in diminishing bone loss. Hence, a thiazide may be the preferred drug when osteoporotic patient also has hypertension and nephrolithiasis [30].

Statins

Statins have been seen to promote osteoclast apoptosis and synthesis activity in osteoblasts. Statins also inhibit mevalonate pathway, increase the gene expression for bone morphoenic protein 2 (BMP-2) and the bone formation. Hence, it seems that statins are going to be the future drug for treatment of osteoporosis [31].

Other sclerosin inhibitors

Sclerosin is produced by osteocytes and inhibits bone formation. In animal studies, treatment with monoclonal antibody that blocks sclerosin resulted in increase in BMD. Inhibitors of sclerosin hold promise as a therapy to bone mass [32].

Integrin antagonists

Adhesion of osteoclasts to bone surface is an important initial step for bone resorption. Intergrin mediates cell and cell matrix interaction. Thus, integrin inhibitors prevent osteoclast interaction with extracellular matrix and hence bone resorption [33].

Cathepsin k inhibitor

Cathepsin k is a cysteine protease that is expressed in osteoclasts. It plays a role in osteoclasts mediated bone resorption. Inhibition of cathepsin k may attenuate bone resorption without concurrent inhibition of bone formation [34].

Fluoride

Fluorides are potent stimulators of osteoprogenitor cells. They have been used in multiple osteoporosis studies with conflicting results, because of the use of varying doses and preparations. Flouride increases bone mass of up to 10%, but no consistent effects have been observed on vertebral or non vertebral fracture. Fluoride remains an experimental agent despite its long history and multiple studies [35].

Stem cell therapy

Mesenchymal Stem Cells (MSCs), obtained from bone marrow, adipose tissue and cord blood have been studied for osteoporosis. These are easily available, devoid of ethical issues, possess immunosuppressant properties, and are multipotent and safe. MSCs differentiate into osteoblasts upon systemic administration. Hematopoietic Stem Cells have also been found to produce osteoblasts [36].

Summary

Osteoporosis can be prevented by Calcium and Vitamin D supplementation along with life style modifications. A lifelong intake of adequate amounts of calcium and vitamin D is essential for optimal bone formation and maintenance. But once the osteoporosis develops, it can be treated with a Bisphosphonate drug, Calcitonin, Teriparatide, Estrogen, Raloxifene, Denosumab, or Strontium ranelate. Most drugs reduce bone resorption while Teriparatide stimulates bone formation and Strontium acts by both the mechanisms to reduce the risk of fractures in patients with osteoporosis.

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