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OSTEOPOROSIS-TREATMENT AND MANAGEMENT

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ABSTRACT
Osteoporosis is a progressive systemic skeletal disease characterized by reduced bone mass/density and micro architectural deterioration of bone tissue. It is a "silent disease" as there are no symptoms prior to a fracture. The prevalence of osteoporosis increases markedly with age. DEXA is regarded as the gold standard technique for diagnosis of osteoporosis. Treatment for osteoporosis should include lifestyle measures including nutrition, exercise and measures to reduce falls. Adequate calcium intake and vitamin D should be provided. Effective pharmacological management strategies should always be implemented where necessary including bisphosphonate such as Alendronate, Etidronate, Risedronate, andraloxifene, strontium ranelate and teriparatide. Postmenopausal osteoporosis may be treated with a bisphosphonate. If bisphosphonates are unsuitable then calcitriol may be considered. Estrogen should only be considered if there is significant risk for osteoporosis and other drugs are not suitable. New biologics agents, Denosumab and Odanacatib are approved for treatment of osteoporosis. Both target osteoclasts to rebalance bone loss and bone building. The prevention of osteoporosis should be considered in early life and should be continued by regular physical activity and a balanced diet.

KEYWORDS: Osteoporosis, Bone Mass Density (BMD), Bone Resorption, Catephsin K Inhibitor, Anti-Sclerostin bodies, Vertebroplasty, Mesenchymal Stem Cells (MSC).

INTRODUCTION
Osteoporosis is a skeletal disorder characterised by low bone density and micro architectural deterioration of bone tissue. This results in an increase in the risk of fracture.[1] The resulting fractures pose a major health problem. Hip, vertebral, and wrist fractures are most commonly affected by osteoporosis. Structure and micro architecture are important aspects of bone strength and essential elements for the assessment of bone mechanical properties. The main structural determinants of bone mechanical strength include width, porosity and shape of the bone. Gradual weakening or thinning out of bones normally occurs with age. The longer we live; the bone mass decreases and we become more prone to fractures. A lot about factors can worsen or lessen the extent of bone loss. Osteoporosis is a very complex disease where many factors influence the rate of bone loss.[2]

Types of Osteoporosis
Osteoporosis is generally divided into primary osteoporosis and secondary osteoporosis. Both the types can occur simultaneously in the same person. The cause of primary osteoporosis is not clearly understood. Primary osteoporosis is divided into postmenopausal (type I) and senile (type II) osteoporosis. Secondary osteoporosis is less common and defined as bone loss occurring due to other diseases, such as Cushing's syndrome or malignancy.

Accelerated or postmenopausal osteoporosis (Type I)
Bone loss is accelerated in women after five to ten years of menopause due to reduced production of the female sex hormone, estrogen. Ten or more years after menopause, accelerated bone loss slows down and approaches the rate of decline observed in older men. In five to ten percent of postmenopausal women, bone loss is severe and leads to fractures before age 75. Postmenopausal osteoporosis most often results in collapsed vertebrae. Other bones, such as wrist bones, are also affected. Type I bone loss occurs in women over six times than in men.

Age-related osteoporosis (Type II)
Age-related osteoporosis occurs in both sexes in women over age 70 and men over age 80. This is evidence that the incidence of fractures increases with the lowering of bone mineral density. Type II bone loss typically results in hip fractures, although fractures occur in other types of bone as well. An underlying disease, a hormonal imbalance or nutrient deficiency may accelerate age-

related bone loss.

Secondary osteoporosis
Sometimes, osteoporosis is a side-effect of another health condition. For example, overproduction of cortisone, as in Cushing Syndrome, abnormally low production of sex hormones, as in hypogonadism can lead to bone loss; certain malignancies, particularly myeloma (a bone marrow cancer), hyperthyroidism and hyperparathyroidism can also result in bone loss. Digestive, kidney, or liver disorders may lead to bone loss.[3]

RISK FACTORS USED FOR ASSESSMENT

Clinical factors

- Age- Increasing age increases fracture probability. Osteoporosis is rare in young adults and middle-aged men.
- Sex- Women live longer than men, and thus may be more likely to develop fractures.
- Bone mineral density- The lower the BMD the higher the fracture risk. Bone mass can be assessed at a number of sites by help of dual energy x-ray absorptiometry (DXA).
- Low body mass index (>19kg/m2)- Low body mass index and weight loss are strongly associated with increased fracture risk.
- Previous fragility fracture, particularly of the hip, wrist and spine.
- Secondary causes of osteoporosis including: Parental history of hip fracture, Current glucocorticoid treatment.
- Rheumatoid arthritis
- Untreated hypogonadism in men and women.
- Type I diabetes
- Hyperthyroidism, Gastrointestinal disease, chronic liver disease.
- Frequent falling
- Alcohol and Cigarette smoking- These two are detrimental to bone. Many factors including reduced body weight, earlier menopause and increased metabolic breakdown can cause osteoporosis. There is an inverse relationship between cigarette smoking and BMD. Consumption of large quantities of alcohol may be detrimental to bone. This might be due to adverse effects on protein and calcium metabolism, mobility, gonadal function, and a toxic effect on osteoblasts.

Physical activity- It has been shown that physical loading and mechanical stress increase BMD and that certain forms of exercise may retard bone loss. Moreover, epidemiological studies have shown that a relationship exists between physical inactivity in the elderly and the risk of hip and vertebral fracture.

Environmental factors: These include Lack of assistive devices, Obstacles in the walking paths, Slippery conditions, Low level lighting, Caucasian or Asian heritage, Genetics.

Medical factors: Some medical factors causing osteoporosis are Arrhythmias, Anxiety, Depression, Poor vision, Orthostatic hypotension, Dehydration, Previous falls, Medications causing sedation such as narcotic analgesics, Vitamin D insufficiency, Malnutrition, Neurological and musculoskeletal risk factors Kyphosis, Weak muscles/sarcopenia etc.[4] Secondary osteoporosis maybe caused due to Steroid therapy and Amenorrhea, Cushing's Syndrome, Anorexia Nervosa, Myeloma, Hyperprolactinemia, Skeletal metastases, Diabetes mellitus, Gastric surgery, Alcoholism, Anticonvulsant therapy. Several medications also lead to osteoporosis. Several medications have been shown to contribute to the development of osteoporosis. Glucocorticoid (or corticosteroids), the leading secondary cause of osteoporosis, decrease bone formation by down regulating osteoblasts and prolonging their life span. In addition, an inhibitory effect on sex hormones influences bone formation. Thiazolidinediones given to persons with diabetes mellitus can lead to osteoporosis by their direct action on bone cell differentiation. Unfractionated heparin given for greater than one year has been associated with decreased bone formation and increased resorption.[5]

PATHOPHYSIOLOGY

To understand the pattern showed by osteoporosis in destruction of bones we must know formation and composition of bones Mechanisms of Bone Formation and Destruction.

Bones are in a continuous state of dissolution and reformation. Two opposing forces occur within the bones to determine their hardness:

- Bone resorption: Destruction of old bone tissue and
- Bone formation: production of new bone tissue.

These two forces occur inside the body. Old bone is dissolved and new bone is formed continuously. This helps in change of shape and size of bone so that it can adapt to the changing shape of the body. Bone resorption initiates the 'bone remodelling cycle' which leads to formation of new bone. However, to maintain bone strength, bone formation must keep up with bone resorption. If bone formation lags behind, bone loss is inevitable. This seems to be what happens in osteoporosis.

Bone Composition
Like other tissues, bones are made up of many cells. However, bone cells lie on the surface of the bone, or are enclosed by calcified bone tissue. The enclosed cells are those which remain active. There are three types of bone cells. All play different roles in bone maintenance:

- Osteoclasts are responsible for bone resorption by dissolving bone minerals and initiation of the bone remodelling cycle.
- Osteoblasts are responsible for bone formation and

completion of the bone remodelling cycle. Osteoblasts form new bone by secreting protein fibers into the cavities produced by the osteoclasts. Calcium salts are responsible for hardening these protein deposits.

- Osteocytes are responsible for maintenance work within bone tissue.

The basic framework of bones is a protein, collagen matrix. Calcium is the major mineral in bone. Bone becomes hard because mineral salts get incorporated into the protein mesh. The predominant mineral salt present in bone is a calcium phosphate salt called as hydroxyapatite. Magnesium, sodium and potassium salts and small amounts of fluoride and chloride are the other inorganic matter present in bone.[6]

Hence, osteoporosis is caused due to the excessive breakdown of bone structure, inadequate bone formation, or an imbalance in the activity between the bone cells responsible for bone remodelling or from the increased number or activity of osteoclasts, the cells of bone resorption and also the decreased number or activity of osteoblasts, the cells of bone formation, on areas of the bone that demonstrate both of these abnormal bone cell characteristics.[7]

DIAGNOSIS

Symptoms are seldom useful to know the presence of osteoporosis before the first fractures occur and by this time bone loss would have already a significant stage. The earliest symptom is pain followed by a fracture. Some fractures may be so minute that they cannot be noticed immediately. However, they add up to and lead to bone weakening. More severe fractures cause more intense pain.

Bone mass is a major determinant of bone strength. Studies have shown an increase in the risk of bone fracture with decrease in the bone density. Several methods are available for the assessment of bone mass. The absolute BMD for a given bone varies with different systems.

Some available bone mass techniques are

Single beam (photon) absorptiometry (SPA), Dual Beam (photon) absorptiometry (DPA), CT (computed tomography) scan, Digital radiography etc.

New imaging techniques for osteoporosis

Given that the majority of vertebral fractures are asymptomatic and that X-rays are not routinely performed unless symptoms are present, it is possible that high-risk individuals may be inadequately identified and remains untreated for osteoporosis. Currently available tests expose the patient to low-level radiation, are time- consuming and can be costly. Hence, new techniques are required.[8]

DEXA Scanning

Bone densitometry by Dual Energy X-Ray Absorptiometry (DEXA) measures the bone mineral density usually at hip and spine. Results may be given as a 'T' score which is the result compared to a "young normal adult" of the same sex or a 'Z' score which is the result compared to that expected for the patient's age and sex. The T score is usually most predictive of the future fracture.

Classification	Bone Mineral Density	T Score
Normal	Within 1 SD of the mean level for a young adult reference population	T score at −1.0 and above
Low bone mass (Osteopenia)	Between 1 and 2.5 SD below that of the mean level for a young adult reference population	T score between -1.0 and -2.5
Osteoporosis	2.5 or more below that of the mean level for a young adult reference population Severe	T score at or below -2.5
Severe or established osteoporosis	2.5 or more below that of the mean level for a young adult reference population	T score at or below -2.5 with one or more fractures

Fracture Risk Assessment Tool Model (FRAX)

FRAX is a recently released, web-accessed fracture assessment tool that has been developed by the World Health Organization. It allows quick calculation of the 10- year likelihood of hip and major osteoporotic fractures (hip, clinical spine, humerus, or wrist fracture) using algorithms. These algorithms integrate the weight of clinical risk fractures for fracture risk with or without information on the BMD. FRAX is a major advance in systematizing fracture risk assessment. However, it has a number of limitations. Important factors that modulate fracture risk, such as propensity to fall, increased bone turnover markers, vitamin D deficiency, medications that accelerate bone loss (such as aromatase inhibitors), and use of osteoporosis therapy, are not included in the model. FRAX also does not consider low spine BMD.[9]

TREATMENT

A detailed history and physical examination together with BMD assessment, vertebral imaging to diagnose vertebral fractures and the WHO-defined 10-year estimated fracture probability test are utilized to establish an individual patient's fracture risk. All postmenopausal women and men aged 50 years and above should be evaluated for osteoporosis risk in order to determine the need for BMD testing and/or vertebral imaging.

Pharmacological Treatment

Calcium supplements

As the major mineral component of bone, calcium plays an indispensable role in bone health and bone serves as a reservoir to help maintain blood calcium. Adequate intakes (AI's) of calcium for different age groups were established by the Food and Nutrition Board of the Institute of Medicine of the National Academies.[15] For those who do not or cannot achieve sufficient dietary calcium intake, supplemental calcium is needed, but even when dietary and supplemental calcium intake is taken into account. AI's for calcium represent the amounts required for adequate calcium retention and bone health in healthy people. Lack of knowledge about the need for calcium and lack of motivation have been associated with not using supplements. There are thus excellent opportunities for pharmacists to help patients achieve calcium adequacy.[10]

Vitamin D supplements

Levels of 25-hydroxyvitamin D <20 ng/mL represent deficiency and between 20 and 30 ng/mL represent insufficiency. Most people worldwide are vitamin D insufficient or deficient which can cause implications for osteoporosis and other health problems. Risk factors for vitamin D deficiency include advanced age, infants exclusively breastfed but not supplemented with vitamin D, persons with dark skin, insufficient sunlight exposure, use of medications that alter vitamin D metabolism (e.g. anticonvulsants) and malabsorption.[11]

Antiresorptive agents Biphosphonates

Bisphosphonates are synthetic analogues of the naturally occurring compound called pyrophosphate and bind strongly to hydroxyapatite, inhibiting bone resorption by inactivating osteoclasts. The majority of primary and secondary osteoporosis treatment involves the use of bisphosphonate therapy. The nitrogen containing bisphosphonates alendronate, risedronate, ibandronate and zoledronate are analogues of inorganic pyrophosphate. The most commonly prescribed oral bisphosphonate is alendronate. If taken properly GI side effects are uncommon.

Selective oestrogen receptor modulators (SERMs)—Raloxifene

Estrogen reduces the risk of hip and spine fractures in postmenopausal women. Raloxifene is a partial oestrogen agonist that acts as an agonist in bone, but an antagonist in other areas of the body such as the uterus and breast. It therefore has positive oestrogen effects in the bones, without other unwanted oestrogen effects elsewhere. It has been shown to reduce deteriorating BMD in women. However, there is an increased risk of venous thrombo-embolic events and hence not much considered.[12]

Strontium ranelate

Strontium, an element directly below calcium in group 2 of the periodic table, is combined with ranelic acid as a carrier to form strontium ranelate. It is taken as a single daily oral dose. Its mechanism of action remains a subject of research, but there is evidence that it increases bone strength by altering bone material properties. Administration of strontium ranelate leads to a substantial increase in BMD at the spine and hip. It is shown to reduce fracture risk in postmenopausal women and in men with osteoporosis, although SR has not been approved by the FDA.[13]

Emerging therapies-Denosumab

Denosumab, a fully humanised antibody to receptor activator of nuclear factor kappa B ligand (RANKL) is a newer antiresorptive agent. RANKL, secreted by osteoblasts, is a major activator of osteoclastic bone resorption and mimics the action of osteoprotegerin.[22] Denosumab is used in the treatment of postmenopausal women at a high risk of fracture, patients having a history of osteoporotic fractures, or patients who have failed or are intolerant to other available osteoporosis therapies. It has been shown to reduce the risk of fractures of the spine, hip, and non-vertebral sites. Side effects are uncommon, but may include skin infections, predominantly cellulitis.[14]

Drugs that Promote Bone Formation Teriparatide

Teriparatide is a recombinant form of parathyroid hormone (PTH). It is currently the only widely available anabolic agent used for osteoporosis. Teriparatide increases renal re-absorption of calcium and enhances intestinal calcium absorption which is useful for the formation of bones. Elevated levels of parathyroid hormone (PTH), as seen in primary or secondary hyperparathyroidism, increase bone turnover and lead to bone loss. Intermittent administration of PTH increases the number of bone forming osteoblasts whereas continuous administration increases the number of bone resorbing osteoclasts. Teriparatide is approved for a maximum of two years of use after which bisphosphonates can be used to retain the benefit accrued.[15]

Combination Therapy

In recent times there has been interest in looking at combination therapies, either treatment given at the same time or following on from each other. Most trials data have assessed the combination of anabolic therapy (teriparatide) with an antiresorptive therapy (a bisphosphonate or denosumab). Combination therapy with teriparatide and raloxifene was found to improve hip BMD compared to teriparatide alone. For patients who had been taking alendronate or raloxifene long term, addition of teriparatide led to larger increases in BMD. A very recent study on patients who had taken alendronate long term adding teriparatide to the regimen was proven to be beneficial. No formal recommendations regarding combination therapy have been formulated, but combination anabolic/antiresorptive therapy will likely continue to be an area of great interest particularly when patients at very high risk are considered.

Novel Therapies

Cathepsin K Inhibitor

Cathepsin K is a lysosomal cysteine proteinase expressed by osteoclasts, and is one of the enzymes that degrade type I collagen, a major component (90%) of bone matrix. Other cathepsins B, L and S degrade collagen in other tissues such as skin and lung, so a Cathepsin K inhibitor has to be selective over these other types in order to avoid side effects. Odanacatib is a highly selective cathepsin K inhibitor. In phase I clinical trials, a half life of 66-93 hours was observed, allowing for once weekly dosing. Because of the direct role of cathepsin K in the production of collagen fragments, interpretation of these bone resorption markers may be different compared to other antiresorptive drugs. Decreases in markers of bone formation were modest and transient compared with those seen with other antiresorptive therapies (e.g., alendronate and risedronate) and were consistent with the non- significant decreases in bone-formation rate and mineralizing surface in the biopsy samples. The phase II study was subsequently extended by a year to look at further efficacy and safety as well as the effects of discontinuation.[16]

Anti-sclerostin antibodies

Sclerostin, an osteocyte-secreted protein, negatively regulates osteoblasts and inhibits bone formation through the LRP5/Wnt signalling pathway. A monoclonal antibody to sclerostin, romosozumab, was administered intravenously to healthy men and postmenopausal women and was shown to increase bone formation markers, along with a dose-related decrease in bone-resorption markers. Romosozumab is a humanized monoclonal antibody that blocks sclerostin from inhibiting osteoblast maturation and function. It has undergone phase I and phase II studies. Phase III studies are currently underway.[17]

TABLE

PHARMACOLOGICAL TREATMENT FOR OSTEOPOROSIS

Generic Drug (Brand Name)	Indications and Dosing	Contraindications	Comments
Alendronate (Fosamax®)	Prevention: 5 mg per day or 35 mg per week; treatment: 10 mg per day or 70 mg per week	Delayed esophageal emptying, inability to sit or stand upright for 30 minutes, hypocalcemia, creatinine clearance <35 mL per minute, hypersensitivity	Firstline treatment option; significantly reduces vertebral and nonvertebral fractures
Risedronate (Actonel®)	Prevention and treatment: 5 mg per day, 35 mg per week, or 75 mg twice monthly	Delayed esophageal emptying, inability to sit or stand upright for 30 minutes, hypocalcemia, creatinine clearance <35 mL per minute, hypersensitivity	Firstline treatment option; significantly reduces vertebral and nonvertebral fractures
Ibandronate (Boniva®)	Prevention and treatment: 2.5 mg per day or 150 mg per month	Delayed esophageal emptying, inability to sit or stand upright for 60 minutes, hypocalcemia, creatinine clearance <35 mL per minute, hypersensitivity	Secondline treatment option; significantly reduces vertebral fractures
Zoledronic acid (Reclast®)	Prevention and treatment: 5 mg (100 mL) infusion once yearly	Hypocalcemia, creatinine clearance <35 mL per minute, hypersensitivity	Firstline treatment option; significantly reduces vertebral and nonvertebral fractures
Calcitonin (Miacalcin®)	Treatment: 200 IU nasal spray per day	Hypersensitivity	Lastline treatment option; significantly reduces vertebral fractures
Raloxifene (Evista®)	Prevention and treatment: 60 mg per day	Past or current history of venous thromboembolic events, pregnancy, hypersensitivity	Second- or thirdline treatment option; significantly reduces vertebral fractures
Teriparatide (Forteo®)	Treatment: 20 micrograms per day subcutaneous injection	Risk of osteosarcoma, hypersensitivity	Significantly reduces vertebral and nonvertebral fractures; use in severe cases and/or if other agents cannot be used/have failed
Denosumab (Prolia®)	Treatment: 60 mg subcutaneous injection every 6 months	Hypocalcemia, immunosuppression, creatinine clearance <30 mL per minute	Firstline treatment option; significantly reduces vertebral and nonvertebral fractures

Surgical treatment

Surgery for treating osteoporotic vertebral fractures usually consists in percutaneous minimally invasive procedures: vertebroplasty and kyphoplasty.

Vertebroplasty

Vertebroplasty is a percutaneous minimally invasive procedure that was first performed in France in 1985. To perform a vertebroplasty, a bone needle is passed through or lateral unilateral or bilateral pedicles until the vertebral body and a small amount of cement of Polymethylmethacrylate (PMMA) or Calcium phosphate-based, mixed with antibiotic and barium or tantalum is pushed into. Once injected, the cement hardens quickly. The procedure is monitored by fluoroscopy. Pain relief after vertebroplasty is reported in 24-48 hours, and can be maintained along with conservative management.[18]

Kyphoplasty

Kyphoplasty is a percutaneous minimally invasive procedure. Patient is positioned in the hyperlordotic (hollow back, anterior tilted) position, then a little cannula is inserted until the vertebral body, and a balloon catheter is passed through it, which is blown to increase the collapsed space and to create a defined cavity, that is

then filled with cement. Relief of pain in 90% of cases was found to be gained in 24-48 hours, and sustained up to 2 years follow-up. Improvement in physical function was reported in 95% of cases.[19]

Conservative treatment

Conservative treatment for vertebral fractures consists in bed rest, analgesics, Non- Steroidal Anti-Inflammatory Drugs (NSAIDs), braces and rehabilitation; but the duration of each of them differs. Although pharmacologic approaches represent the cornerstone of treatment, some patients cannot comply with medication regimens, particularly because of potential adverse effects, but also because some patients cannot afford certain medication options. For such patients non-pharmacologic or conservative management may be helpful.

MESENCHYMAL STEM CELL BASED THERAPY

Cell therapy has attracted considerable clinical attention for the treatment of various diseases for many decades. Stem cells are believed to be an ideal source of cell replacement therapy for bone diseases due to their properties of self-renewal and plasticity, which can repair or regenerate damaged tissues. Candidate stem cell types include embryonic stem (ES) cells, induced pluripotent stem (iPS) cells and somatic stem cells such as MSCs. The use of ES and iPS cells is limited due to ethical issues and virus-based derivation methods. It seems likely that the use of MSCs overcomes the limitations and is more practical in other disease methods. In recent years, MSCs have become dramatically interesting for the treatment of osteoporosis. MSCs have the ability to self-renew and grow into specific tissues, such as cartilage, bone and adipose tissues. Human MSCs are defined by their phenotypic expressions such as CD105 and CD73. With regard to the pathogenesis of osteoporosis, resulting in bone mass reduction, transplantation of MSCs might promote new bone formation and strengthen the bone, contributing to improvement of bone quality and prevention of fractures.

After transplantation, MSCs contribute to bone formation by two possible mechanisms of action:

[1] MSCs homing to a damaged site or pathologic area and then differentiating into bone-forming cells to repair the degenerated tissue and

[2] MSCs acting in a paracrine manner by secreting certain growth factors that modify the environment and recruit resident cells to repair the degenerated tissue.

Sources of mesenchymal stem cells: advantages and disadvantages.

Bone marrow-derived MSCs

Bone marrow is the most commonly used tissue source of adult MSCs. Bone marrow-derived MSCs (BM-MSCs) have been extensively studied in bone regeneration and repair due to their high efficiency in osteogenic differentiation. BM- MSC transplantation is applicable in the treatment of osteoporosis. Ichioka et al. demonstrated that normal allogenic BM-MSCs could increase trabecular bone and attenuate the loss of BMD after being directly injected into the bone marrow cavity of an osteoporotic mouse model that exhibits age-dependent osteoporosis. However, use of autologous BM-MSCs for osteoporosis treatment in elderly patients is limited due to the age-related decline in the overall BM-MSC number.[20] Recently, use of autologous BM-MSCs for the treatment of osteoporosis has been performed in clinical trial study. Autologous BM-MSCs were collected 30 days before infusion, and the cells were cultured under GMP conditions to establish the dose range. In this study, the cells were subjected to the process of fucosylation before intravenous infusion into osteoporosis patients. However, this study is still in the process of recruiting participants and is thus not yet completed.

Adipose tissue-derived MSCs

Adipose tissue provides an attractive source of MSCs that has become increasingly popular in many stem cell applications. Adipose tissue-derived MSCs (AD-MSCs) are isolated from white adipose tissues via a minimally invasive approach and can be expanded and differentiated into classical mesenchymal lineages involved in adipogenesis, osteogenesis, and chondrogenesis. AD-MSCs are more easily isolated and more abundant and produce higher yields in terms of cell number compared with BM-MSCs. However, the yield of AD-MSCs and their proliferative and differentiation capacities vary depending on the tissue harvesting site and the age of the donor. For application in cell therapy for osteoporosis, AD-MSCs were reported to function as an effective autologous cell-based approach for the treatment of osteoporosis. SAMP6 osteoporosis mice showed significant improvement in several trabecular bone parameters. The effect of human AD-MSC therapy likely occurs in a paracrine manner by the secretion of various bone-related growth factors, e.g., hepatocyte growth factor, BMP-2, and RANKL, and extracellular matrix (ECM) proteins, e.g., fibronectin, which might promote osteogenic differentiation, bone remodelling and repair in the recipients.[21] Recently, a clinical trial has studied the use of human AD-MSCs for the treatment of proximal humeral fractures in individuals over 50 years old, representing a model for fractures of osteoporotic bone. Clinical/radiological follow-up was performed after 6, 9 and 12 months, and functional assessment was performed after 6 weeks and 6 and 12 months using the Quick DASH score and the Constant score. Unfortunately, the study was terminated, and no results are available.

Perinatal-derived MSCs

Although BM- and AD-MSCs are effective sources, the therapeutic potential of these adult MSCs can be affected by the donor's lifestyle and age. Perinatal tissues are alternative sources of MSCs that have attracted growing interest in bone regenerative medicine. Not only are

these cells younger than adult MSCs, but perinatal-derived MSCs also having the major advantage of an easy and non-invasive harvesting procedure without any risk to the donor. A comparative study of MSCs isolated from different perinatal tissue sites, including the umbilical cord, umbilical cord blood (UCB), amnion, and chorion, revealed that these tissues exhibit similar characteristics to BM-MSCs, including similar phenotypic features, growth properties, differentiation capacities, secretory protein profiles, and low immunogenic properties.[22] However, these stem cell sources are still limited by their low capacity to differentiate compared with BM- and AD-MSCs, and they have not been clearly examined in preclinical studies.

Placenta-derived MSCs

The placenta is an easily accessible source of perinatal MSCs that provides a high yield of MSCs. Placenta-derived MSCs (PL-MSCs) exhibit adipogenic, osteogenic and neurogenic differentiation capacities. Sanvoranart et al. demonstrated that PL-MSCs responded to bortezomib, a chemotherapeutic agent that improves osteolytic lesions, via enhancement of osteogenic differentiation, similarly to BM-MSCs.[23] This finding suggests the potential therapeutic application of PL-MSCs in osteopenia and osteoporosis patients.

Umbilical cord-derived MSCs

The umbilical cord contains various cell types, including vessels, connective tissues, and Wharton's jelly. After isolation, these heterogeneous cells are observed to possess differential expressions, but not variable capacities to differentiate into chondrogenic, adipogenic, and osteogenic lineages. In vivo bone formation by umbilical cord-derived MSCs (UC-MSCs) was demonstrated by Diao et al., who loaded human UC-MSCs into mice subcutaneously and found that the human UC- MSCs could efficiently form bone after implantation for 12 weeks.[24]

Wharton's jelly-derived MSCs

Wharton's jelly is the mucoid connective tissue that surrounds the umbilical cord vein and protects it. Fibroblast-like cells were first isolated from Wharton's jelly by McElreavey et al. in 1991. These fibroblast-like cells were characterized as MSCs due to their expression of MSC phenotypic markers and their capacities to differentiate into osteogenic, adipogenic, and chondrogenic lineages. A comparative study of human derived-MSCs demonstrated that Wharton's jelly-derived MSCs (WJ- MSCs) exhibited the strongest immunomodulatory and immunosuppressive properties which makes them more applicable for clinical use as cell therapy. The capacity of WJ-MSCs to undergo osteogenic differentiation in vitro and new bone formation in vivo was similar to that of other MSCs isolated from canine bone marrow, adipose tissue, and UCB.[25] Hence, WJ-MSCs can potentially be used in clinical bone engineering for further treatment of bone defect diseases.

PREVENTION AND MANAGEMENT

The most important measure in the management of osteoporosis is treatment of the underlying cause. Various preventive treatment measures have been described below.

Non-modifiable	Potentially Modifiable
Advanced age (≥50 years) Female sex White or Asian ethnicity Genetic factors as family history of osteoporosis Dementia	Cigarette smoking Low body weight (<58 kg or 127 lb) Recurrent falls Inadequate physical activity Estrogen deficiency Drugs Alcohol use Early menopause Prolonged premenopausal amenorrhea Androgen or estrogen deficiency Calcium deficiency Poor health

Prevention of osteoporosis focuses on nutritional and lifestyle changes. The goals include

- Acquiring maximal peak bone mass
- Maintaining this bone mass for as long as possible

Increasing awareness of modifiable risk factors for osteoporosis through patient education is important.[26]

Exercise: Exercises are another way to maintain BMD, prevent the progression of osteoporosis and reduce the risk of developing bone fractures. A combination of weight bearing and strength training exercises are most effective. Even just walking or jogging regularly can help prevent osteoporosis. Exercise habits should be consistent, at least three times a week as more substantial effect on bone mass is likely if exercise is continued over a long period of time. The beneficial effect wanes if exercise is discontinued.[27]

Prevention of falls: Falls are the precipitating cause for most osteoporotic fractures; some measures should be taken to prevent falls in the household, particularly for patients who are frail. Preventing falls prevents fractures. Lowering the risk of falls includes checks on vision, hearing, adverse effects from certain medications, safety at home and during exercise etc.[28]

Diet: Adequate calcium intake is necessary for the formation of bones and its maintenance throughout life. Calcium is easily absorbed from dairy products hence, these are the best sources. In addition, orange juice, cereals, bread and soy-based drinks may contain calcium. Calcium supplements are required when dietary calcium is inadequate. Excess caffeine intake is associated with reduced calcium absorption or excess excretion. Vitamin D is increasingly being recognized as a key element in overall bone health and muscle function. It plays a significant role in bone health, calcium absorption, balance and muscle performance. Many other nutrients and dietary factors may be important for long-term bone health and the prevention of osteoporosis. Among the essential nutrients, other elements such as zinc, copper, manganese, boron, vitamin A, vitamin C, vitamin K, the B- vitamins, potassium and sodium are required. Magnesium is one of a number of nutrients found in fruits and vegetables, which contribute to an alkaline environment and may promote bone health by a variety of mechanisms.[29]

CONCLUSION

Osteoporosis is a potentially debilitating disease with substantial human, economic and social implications. Recent advances in prevention, testing and risk assessment for osteoporosis have proceeded apace with development of new therapies to reduce fractures in those at risk. The FRAX algorithm and recent recommendations from national and international bodies regarding prevention and management of osteoporosis have provided helpful guidance to health care practitioners in many disciplines, including pharmacists. Newer treatments (odanacatib, romosozumab, and abaloparatide) are likely to be used as second or third line treatments after an initial period of 3 to 5 years on a bisphosphonate, to try and increase BMD and counter concerns about continuing suppression of bone remodelling and possible implications for atypical fracture. Better understanding of the benefits of “routine” elements of care, such as vitamin D therapy and lifestyle changes, are very welcome. It is important to analyze the difference in the mode of action, efficacy in fracture prevention, and safety profiles of these agents in order to develop safe and effective management of patients with osteoporosis. Development of new therapeutic strategies and better use of established drugs, including monitoring for recently appreciated risks, provides pharmacists with new opportunities to play important roles in helping prevent fractures in their patients at high risk for fracture.

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