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Review
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Metabolic Bone Diseases and New Drug Developments

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Abstract

Metabolic bone diseases are serious health issues worldwide, since several million individuals over the age of 50 are at risk of bone damage and should be worried about their bone health. One in every two women and one in every four men will break a bone during their lifetime due to a metabolic bone disease. Early detection, raising bone health awareness, and maintaining a balanced healthy diet may reduce the risk of skeletal fractures caused by metabolic bone diseases. This review compiles information on the most common metabolic bone diseases (osteoporosis, primary hyperparathyroidism, osteomalacia, and fluorosis disease) seen in the global population, including their symptoms, mechanisms, and causes, as well as discussing their prevention and the development of new drugs for treatment. A large amount of research literature suggests that balanced nutrition and balanced periodic supplementation of calcium, phosphate, and vitamin D can improve re-absorption and the regrowth of bones, and inhibit the formation of skeletal fractures, except in the case of hereditary bone diseases. Meanwhile, new and improved drug formulations, such as raloxifene, teriparatide, sclerostin, denosumab, and abaloparatide, have been successfully developed and administered as treatments for metabolic bone diseases, while others (romososumab and odanacatib) are in various stages of clinical trials.

Key Words: Metabolic bone diseases, Osteoporosis, Osteomalacia, New drugs, Odanacatib

INTRODUCTION

The progress of metabolic bone diseases (MBDs) around the world has been steadily increasing in recent times due to a significantly lower intake of calcium, phosphorus, and vitamin D, which leads to nutritional deficiencies that play a major role in these diseases (Gennari, 2001; Hossein-nezhad and Holick, 2013). MBDs are a kind of endocrine disorder that have secured third place in the list of most common human diseases, after diabetes and thyroid disorder, and affect more than 200 million individuals worldwide (Albahri *et al.*, 2021). In India, more than 50 million people suffer from MBDs (Srivastava and Flora, 2020). The most common and familiar MBDs that occur widely around the world encompass osteoporosis, primary hyperparathyroidism (PHPT), osteomalacia (tumor-induced), and fluorosis disease (Fig. 1) (Bonakdarpour, 2009). These mostly affect elderly females, followed by elderly males. Unfortunately, people are unaware of the complications of these MBDs and ignore the primary related symptoms until they cause bone fracture (Vondracek and Linnebur, 2009; Swanson *et al.*, 2015).

Poor nutritional conditions in pregnant females have also been shown to have a significant influence on the cause of MBDs. In children, MBDs can cause sequential developmental abnormalities, skeletal abnormalities, non-traumatic fractures, and functional limitations of motor growth and function (Skowrońska-Jóźwiak and Lorenc, 2006; Cavalier *et al.*, 2016). The underlying reason for MBDs determines a remedy; early diagnosis and treatment of lifestyle factors are critical for an individual's bone health (Thanh *et al.*, 2021). Bone mineral metabolism necessarily requires a well-balanced, rich diet, with vitamin D and calcium, as well as moderate exercise (Chinoy *et al.*, 2019). Some readymade forms of nutritional supplements can restore the shortage of calcium, phosphorus, and vitamin D in people suffering from these diseases (Bonakdarpour, 2009); thus, special osteoporosis medications and attention to diet can slow down bone loss and, in certain instances, restore the lost skeletal structure. Hence, this review attempts to cover the current state of MBDs, and the emergence of novel and effective medications for their treatment.

With annual healthcare expenses of more than $30 billion

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for MBDs worldwide and a predicted threefold increase in such costs over the next 40 years, the development of integrated fracture prevention strategies is critical (Peraza-Delgado *et al.*, 2020). The skeletal accretion in MBDs occurs during adolescence, when there is a significant rise in bone density. Maximum bone density is typically reached upon adolescence and well into the third decade of life. Even by the age of 22, most people have achieved almost all of their skeletal growth (Cooper *et al.*, 2006; Levine, 2012). During menstruation, osteoporosis generally accelerates over 5 to 8 years, with an annual 2% to 3% damage of trabecular and 1% to 2% damage of cortical bone (Kim *et al.*, 2015). Males and females each lose bone mass as they age, with females gradually losing 50% of their trabecular and 30% of their cortical bone over their lifetime, while men lose two-thirds of such quantities (Drake *et al.*, 2015). MBDs were previously believed to be a silent disease that occurred naturally as part of the aging process. The development of skeletal densitometry has created an opportunity to recognize patients precisely and experimentally at high risk for osteoporosis, allowing the implementation of treatment and prevention, to minimize the occurrence of fractures (Marsh *et al.*, 2011; Sözen *et al.*, 2017). Bone seems to be a metabolically active tissue, and there is indeed a constant process of osteoclastogenesis and regeneration in fully grown bone. Osteoblasts are in charge of bone matrix synthesis, while osteoclasts are in charge of bone resorption (Lopes *et al.*, 2018). The importance of osteocytes is becoming more widely recognized. Regular bone formation, metabolic activity, and repair are dependent on the collaborative effort of such cells and the integrity of the calcium and phosphate homoeostatic processes, which also mainly involve parathyroid glands and FGF23, as well as vitamin D (Bergwitz and Jüppner, 2010; Rivadeneira and Mäkitie, 2016). MBDs are usually caused by an individual's internal malformations in skeletal cellular components or by anomalies in calcium and phosphorus homoeostatic processes (Bonakdarpour, 2009), with osteoporosis being the most common. A generalized decrease in bone mass results from an imbalance between the rates of osteogenesis and osteoclast, which can have numerous causes, the most significant of which is estrogen insufficiency in postmenopausal women (Tarantino *et al.*, 2021). Osteomalacia is a mineralization deficiency caused by the lack of calcium or phosphorus, or by deficient osteoblast activity (Anderson *et al.*, 2005). CKD-MBD is a complex bone condition that occurs in patients with renal impairment, while Paget disease is an unfamiliar epidemiological condition characterized by massively increased osteoclastic action and dysfunctional bone regeneration (Polyzos *et al.*, 2018).

OSTEOPOROSIS

Every year, osteoporosis causes over 8.9 million bone cracks globally, with an osteoporosis fracture currently occurring every 3 seconds (Chinoy *et al.*, 2019). According to the WHO, osteoporosis globally affects nearly 6.3% of adults over the age of 50 and 21.2% of women in the same age group (Yoshimura *et al.*, 2017). According to the above estimates, nearly 500 million males and females are affected, based on global male and female populations. Osteoporosis affects 82 million people in Europe, the United States, and Japan. During the year 2000, about 9 million unique osteoporosis fractures occurred, with 1.6 million occurring just at the hip, 1.7 million occurring just at the forearm, and 1.4 million occurring as medical vertebral fractures (Hernlund *et al.*, 2013; Shane *et al.*, 2014). Europe and the United States account for 51% of all fractures, with the remaining portion mostly occurring in the Western Pacific and the region of Southeast Asia (Curtis *et al.*, 2016). Global hip fractures are expected to rise by 310% in males and by 240% in women by 2050, compared to 1990

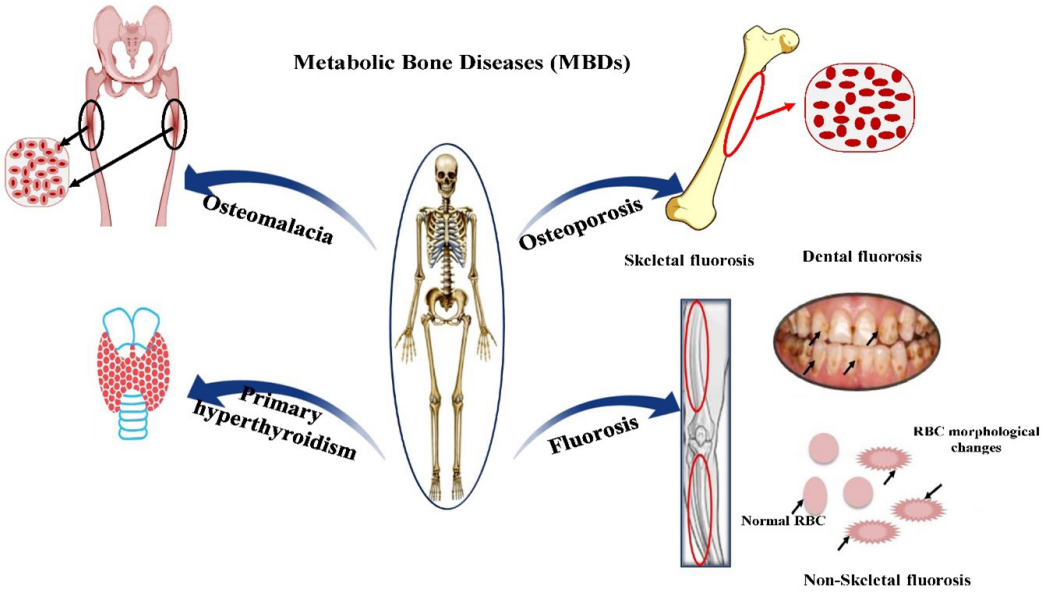

Fig. 1. Most familiar metabolic bone diseases (MBDs). The most common MBDs recognized among the global population are osteomalacia, osteoporosis, primary hyperthyroidism, and fluorosis, which are caused by abnormalities in essential minerals such as Ca, P, and vitamin D, resulting in loss of bone mass and structure.

(Azizieh, 2015). In 2010, it was projected that 158 million people were at risk of osteoporosis, and changing demographics indicate that such figures will more than double by 2040 (Azizieh, 2015). One in every three women over the age of 50 will suffer osteoporosis cracks, as will one in every five men over 50 (Tarantino *et al.*, 2013). Females account for 80%, 75%, 70%, and 58% of arm, humerus, hip, and spine cracks, and for 61% of osteoporosis fractures overall, with a female-to-male ratio of 1.6 (Curtis *et al.*, 2018). Meanwhile, patients aged 65 and above account for nearly 75% of hip, spinal column, and distal arm cracks.

A 10% deterioration of bone density in vertebrae doubles the chance of bone fractures; while a 10% reduced bone density in the hips could lead to a 2.5-fold significantly increased risk of bone fracture (Leib *et al.*, 2011). The probability of hip, forearm, and spinal fractures requiring medical attention is roughly 40% over a lifetime, compared to the risk of developing cardiovascular disease (Leib *et al.*, 2011; Chinoy *et al.*, 2019). Osteoporosis, which means "porous bone," is a condition in which the structure within bones thins (Fig. 2) to the point where a fracture can result from even a slight fall or hit, against a vehicle door or furniture, for example (Azizieh, 2015). A fracture can occur anywhere on the skeleton, although wrist, hip, and spinal cracks seem to be the most frequent.

Nonetheless, a team of specialized cells regularly updates the tiny structure of collagen (a specific protein), while minerals, such as calcium, maintain healthy bones throughout our lives (Chinoy *et al.*, 2019; Kim *et al.*, 2021; Klemmer *et al.*, 2021). Old bone regularly gets broken and replaced with new bone. Until about the age of 25, this process adds as many bone cells as it subtracts, resulting in increased bone density (Curtis *et al.*, 2016; Ciobanu *et al.*, 2021), and bone mass stays stable between the ages of 25 and 50, with equal quantities of osteogenesis and osseous breakup (Swanson *et al.*, 2020). After the age of 50, bone fractures outpace bone formation, and osteoporosis frequently accelerates, especially during menopause. Because women's bones have always been typically more petite and less thick than men's bones, women have an increased high risk of fracture (osteoporosis) and low bone density (osteopenia). This risk rises during menstruation, when levels of bone-building estrogen fall, but men are also at risk (Vijayakumar and Subramanian, 2010a; Ackerman and Misra, 2011). A family background of osteoporosis-related cracks increases the likelihood of developing osteoporosis in both sexes.

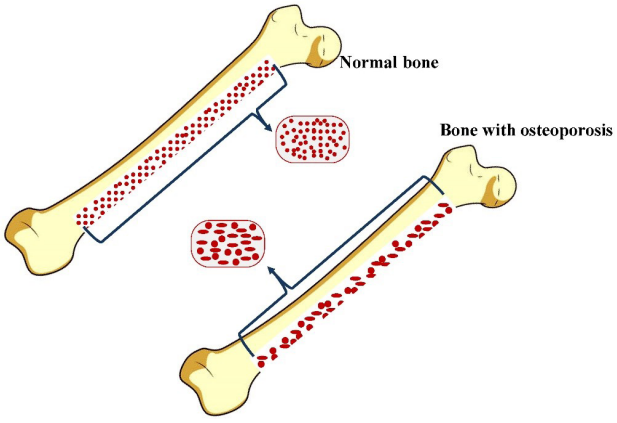

Fig. 2. Bone with Osteoporosis. Osteoporosis (silent disease) causes the bones to become brittle and fragile due to tissue loss, weakening the bones at specific sites (e.g. hip, spine, wrist, and so on) and causing them to break easily.

PRIMARY HYPERPARATHYROIDISM (PHPT)

Primary hyperparathyroidism (PHPT) seems to be a frequently diagnosed bone deformity, with a wide range of symptoms. The most typical symptoms seem to be bone pains, broken bones, kidney stones, gall stone disorder, and pancreatitis, whereas patients living in countryside appear to be symptomless (Zheng *et al.*, 2021). PHPT is characterized by elevated calcium levels, reduced phosphate levels, and enhanced iPTH (intact parathyroid hormone) levels (Al-Azem and Khan, 2012) and is occasionally attributed to low or unidentifiable parathormone (PTH) levels, which could be due to mutated PTH efflux or even PTHrP efflux by hypothyroidism adenoma (Cavalier *et al.*, 2016). In such a case, deciding whether to proceed with surgical intervention is challenging, as the critical condition of PHPT can cause inflammation, kidney cysts, hypertension, bisphosphonates, nephrocalcinosis, obesity, dehydration, insulin resistance, tubular damage in the kidney, kidney stone formation, chronic kidney disease, and increase cardiovascular risk (Fig. 3) (Komoroski *et al.*, 2014; Konda *et al.*, 2020).

CAUSES OF PHPT

As a result of decreased calcium levels, the parathyroid glands secrete hormones, and these hormones are secreted in PHPT as a result of overactivity (Tay *et al.*, 2018). Steadily increasing parathyroid hormonal changes cause the vertebrae to discharge the most calcium into the blood, resulting in el-

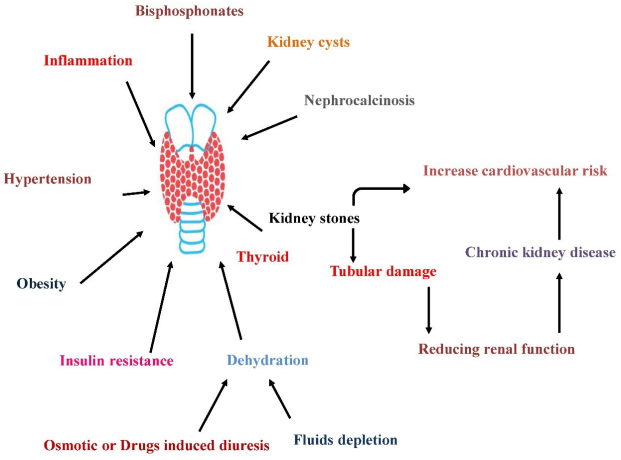

Fig. 3. Clinical complication associated with Primary hyperparathyroidism (PHPT). The imbalanced thyroid hormone condition causes a slew of health issues such as obesity, hypertension, chronic kidney disease, kidney stones, and so on. Such health complications can be managed through a well-balanced nutritional supplementation of the diet.

evated intracellular calcium (hypercalcemia), with increased parathyroid hormone and hypercalcemia being the clinical symptoms of PHPT (Tay *et al.*, 2018). Thus, calcium is essential for bone formation and general health, whilst also being involved in the heart muscle, muscular contractions, blood coagulation, and nerve and signal transmission (Brini *et al.*, 2013). The benign tumors termed adenocarcinomas seem to be the most frequent cause of PHPT (Al-Azem and Khan, 2012). Single adenomas may differ in the four individual parathyroid glands, although numerous adenomas can be established in numerous parathyroid glands, with the negatively affected gland(s) becoming overly active as a result of the adenoma. Numerous gland hyperplasias account for approximately 6-12% of all cases (Gopinath and Mihai, 2011; Arumugam *et al.*, 2016).

The enlargement of numerous parathyroid glands distinguishes the above situation due to an increased rate of cell propagation. Several gland hyperplasias can occur at random (sporadic) or as part of a wider genetic disorder (Lopes *et al.*, 2018). Meanwhile, dual adenomas contribute to around 2-5% of all adenomas. Researchers are baffled as to why adenomas occur in the parathyroid glands. They emerge intermittently in most cases, and there is typically no personal history of such disease. Genetic mutations can sometimes play a role in the progression of PHPT (Wei and Harari, 2012; Ramakrishnan and Vijayakumar, 2017); in intermittent aspects, such gene mutations emerge after embryo fertilization and are obtained rather than inherited.

Numerous causative mutational activities, respectively sporadic and genetic inheritance, have now been described. Inherited PHPT accounts for around 10% of all PHPT case scenarios and can appear alone or as part of the syndrome (McDonald *et al.*, 2015). Genetically inherited PHPT has greater efficacy and a higher proportion of multiglandular active participation (Hossein-nezhad and Holick, 2013). The much more common varieties seem to be based on the constitutional genetic defects of the tumor suppressor genes, such as MEN1 and CDC73, and the calcium receptor gene CASR (Juhlin and Erickson, 2021). In benign parathyroid tumors, multiple associated mutations and potential epigenetic processes have been distinguished. MEN1 abnormalities seem to be prevalent in benign parathyroid tumors, whereas CDC73 mutations are found in 70% of hypothyroidism carcinoma cells, but in only just around 2% of hypothyroidism adenomas (Blau and Simonds, 2021). Thyroid cancer is uncommon, accounting for less than 1% of all PHPT case scenarios and 0.005% of all forms of cancer. It can occur on its own or as part of a huge genetically inherited syndrome. Meanwhile, hypothyroidism melanoma affects approximately 15% of HPT-JT patient populations (Scollon *et al.*, 2017).

Numerous supplementary genetics and genotype-phenotype co-integration are likely to be discovered in the future (Kim *et al.*, 2015). Radiation, particularly as a result of therapy in early life, has now been recognized as a risk factor for the development of PHPT, although there are contradictory reports around the higher risk of developing PHPT following radioactive iodine treatment for hyperthyroidism (Vijayakumar and Subramanian, 2010b; Nilsson, 2019). In roughly one-quarter of cases, lithium, a gold-based standard treatment for bipolar disorder, causes hypercalcemia, and its increased concentration necessitates frequent monitoring, as lithium-associated PHPT can manifest as a single adenoma or as a multiglandular disorder.

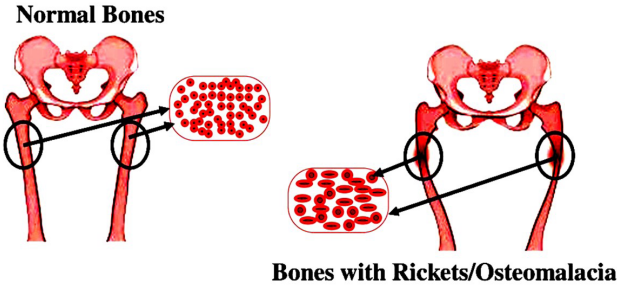

Fig. 4. Bone with Rickets/Osteomalacia. Skeletal muscle soreness and vulnerability may occur as a result of the patient`s bone softening. The lower back, femur, hips, thighs, and rib bones are among the most commonly affected areas in osteomalacia.

RICKETS/OSTEOMALACIA

Osteomalacia is a characterized softening of the skeletal system that is most commonly caused by a severe vitamin D deficiency. Softening of the vertebrae in children and adolescents with osteomalacia can cause bends during development, particularly in the weight-bearing skeletal system of both legs (Fig. 4) (Morgan *et al.*, 2020), whilst cracks can occur as a result of osteomalacia in older individuals. Therapies for osteomalacia entail receiving sufficient vitamin D and calcium, which are both needed to harden and increase bone strength and to treat any underlying conditions that may be causing the condition (Knechtle *et al.*, 2021).

The global prevalence of osteomalacia is rising in poor and developing countries, and even in high-income nations. Fundamental calcium deficiency manifests not only as decreased bone mineralization (rickets and osteomalacia), but also as hypocalcemic seizure activity, tetany, and hypertrophic cardiomyopathy, which can lead to heart failure and death (Uday and Högler, 2017). Untreated osteomalacia associated with death in children is as high as 25%. As a result, clinically visible osteomalacia is suggested to be the “tip of the iceberg”, while the real responsibility of sub-clinical rickets and osteomalacia remain uncertain (Haboubi and Jones, 2007). Calcium deficiency is affected by various factors: a lack of calcium absorption and a lack of vitamin D. Vitamin D deficiency is widespread in Europe, affecting approximately 18% of inhabitants during the winter, though dark-skinned ethnic minorities are at a 3-71 times greater risk (Cashman *et al.*, 2019; Natesan and Kim, 2021a). The rising prevalence of vitamin D deficiency reflects the trend in osteomalacia, with dark-skinned people being more vulnerable.

CAUSES OF RICKETS/OSTEOMALACIA

A flaw throughout the bone-maturing system causes osteomalacia. Calcium and phosphate are minerals that the body seems to use to develop strong bones (Anderson *et al.*, 2005). If insufficient of these mineral resources are obtained in the diet or if the body does not physically absorb these minerals properly, osteomalacia develops (Cashman *et al.*, 2019). In-

adequate vitamin D levels also lead to osteomalacia. Sunlight causes vitamin D to be produced in the skin (Uday and Högler, 2017), while daily nutritional vitamin D is typically obtained from foods that have this vitamin added, such as cow's milk. People who live in areas with constrained sunlight and those that eat a balanced diet with lower levels of vitamin D are at risk of developing osteomalacia (Morgan *et al.*, 2020).

Globally, the primary reason for osteomalacia is a deficiency in vitamin D. Usually, digestion of meals in the stomach leads to the discharge of calcium and other mineral deposits, which are then absorbed in the intestinal wall (Knechtle *et al.*, 2021). Gluten, a protein found in wheat, barley, and rye, can damage the small intestine lining, with a ruptured lining preventing proper nutritional absorption and leading to vitamin D and calcium deficiency (Hossein-nezhad and Holick, 2013). Thus, these organs play a role in the activation of vitamin D. Renal or hepatic problems can also impair the ability to produce active vitamin D, while some seizure medications, such as phenytoin and phenobarbital, can also result in significant vitamin D deficiency and osteomalacia (Ramya *et al.*, 2015; Rivadeneira and Mäkitie, 2016).

FLUOROSIS

Fluorosis is a clinical disorder characterized mainly by the condensation of fluorides in the body's hard and soft tissues (Sellami *et al.*, 2020). It is not caused entirely by a surplus of fluoride consumption, and numerous other factors have been found to influence the emergence of fluorosis in humans (Sahu *et al.*, 2018). It is distinguished by tooth discoloration and crippling diseases and has been documented worldwide, with 22 countries in the systemic phase, and India and China by far the worst affected (Petrone *et al.*, 2013). There are three types of fluorosis: dental fluorosis, skeletal fluorosis (osteofluorosis), and non-skeletal fluorosis (Fig. 5). Dental fluorosis is more prevalent in childhood, while people in their third and fourth decades can develop skeletal fluorosis (Akuno *et al.*, 2019). Meanwhile, there are no age-related factors associated with non-skeletal fluorosis, which necessitates far elevated and prolonged fluoride exposure. Skeletal fluorosis seems to be endemic in some regions: according to the WHO, approximately 2.7 million people in China have a crippling pattern of skeletal fluorosis (Rasool *et al.*, 2018), while 20 provinces in India have now been distinguished as endemic regions, with approximate 60 million people suffering, 6 million handicapped, and developing a neurological disease as a result (Sanghi *et al.*, 2021).

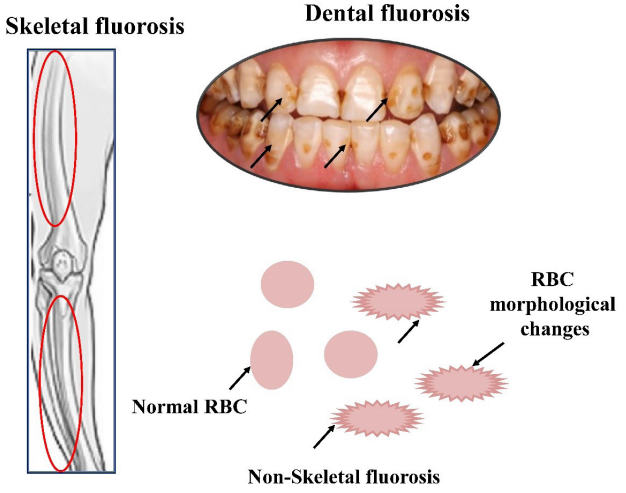

Fig. 5. Various forms of fluorosis. The skeletal and non-skeletal fluorosis can affect the bones and joints due to extended exposure to an elevated quantity of fluoride and causing additional discomforts such as arthritis, osteoporosis, chronic joint pain, and so on.

Children raised in high fluoride regions are more likely to develop dental discoloration that could be seen in deciduous teeth. At first, gleaming, perfect teeth become dull, and yellow-white patches appear upon the affected surfaces (Petrone *et al.*, 2013). These spots slowly turn brown (Fig. 5) and clump close towards the edge of the tooth. Eventually, the entire tooth becomes black, punctured or perforated, and might be chipped off. Skeletal fluorosis tends to affect both the young and old. Extreme pain, backbone stiffness, joints, and solidity in the hip bones are all possible symptoms of calcium deficiency related to high fluoride consumption (Sahu *et al.*, 2018).

Paralysis is caused by blockage of the spinal column and vertebral column foramen and stress on the nervous system in skeletal fluorosis (Sellami *et al.*, 2020). There is compelling proof of engagement of skeletal muscles, erythrocytes, G-I mucosa, ligaments, and spermatozoa in excess fluoride consumption (Akuno *et al.*, 2019). Actin and myosin fibers have been damaged in fluorosed muscles, and mitochondria lose structural stability, indicating a lack of muscular energy. With an elevated fluoride intake, the erythrocyte outer layer loses calcium. Ingesting high fluoride levels in water and food also causes non-ulcer dyspeptic complaints (Petrone *et al.*, 2013). The skeletal lesions are characterized by various degrees of osteosclerosis, osteomalacia, and osteoporosis, along with the emergence of exostoses. Secondary hyperparathyroidism is seen in a percentage of cases, along with characteristic osseous alteration.

CAUSES OF FLUOROSIS

Fluoride is an accumulated toxic substance that can affect bone tissue accumulation and resorption. It also has an impact on bone mineral metabolism, known as homeostasis (Tay *et al.*, 2018). The total amount of fluoride ingested seems to be the primary factor determining the medical course of a disease that is characterized by immobilization of axial skeleton joint surfaces and major extremity joints (Petrone *et al.*, 2013). The main cause of fluorosis seems to be fluoride in drinking water, which is poisonous to health if the concentration exceeds 1.5 mg/L. Water's alkaline pH encourages fluoride absorption (Akuno *et al.*, 2019), while nutrient calcium decreases fluoride absorption, and calcium-rich water reduces fluoride's toxic effects, which are achieved by trace metals such as molybdenum (Akuno *et al.*, 2019). Fluorosis causes changes in hormones that are required for bone mineral metabolism. Meanwhile, the kidney seems to be the main organ of fluoride elimination (Ackerman and Misra, 2011). The variables that impact the result of fluorosis are age, gender, nutritional calcium supplementation, intensity and time of fluoride consumption, and the efficacy of the kidney and liver in fluoride processing (Albahri *et al.*, 2021; Natesan and Kim, 2021b).

Environmental factors also play an important role in fluorosis, including relatively high temperature, reduced rainfall, low humidity, fluoride-rich subsoil rocks, foods from high fluoride belts, tropical climate, and contamination from aluminum ores (Bonakdarpour, 2009; Akuno *et al.*, 2019).

PREVENTION, POSSIBLE TREATMENT, AND DRUG DEVELOPMENT FOR MBDS

It is not too early to begin considering bone mineral density maintenance, and the following steps can aid in the prevention of MBDs:

An adequate intake of calcium prevents fracture risk. There has recently been a debate concerning the potential connection with calcium supplements, as well as vascular calcification, which was seen in one investigation but has not been seen in several other studies involving calcium and vitamin D (Bonakdarpour, 2009).

Everybody should fulfill, but not exceed, the daily recommended allowances, with the following calcium levels being required: 1,000 milligrams per day for women aged 50 to 70 and for men aged 70, which can be obtained through food or supplements (Ethgen *et al.*, 2016). Calcium-rich foods contain other valuable compounds for bone strength, such as protein and Mg, and can enable calcium requirements to be reached. Calcium-rich foods include: low-fat or fat-free milk or yogurt (300 mg per cup), leafy greens (100 mg in 1 cup cooked kale), legumes (91 mg in 1 cup of white beans, 40 mg in 1 cup of pinto beans, and 23 mg in 1 cup of black beans), cereals, and orange (Van Horn et al., 2016). Meanwhile, supplements are an excellent alternative for those who cannot achieve their calcium requirements through diet alone (Uday and Högler, 2017).

Sufficient vitamin D aids calcium absorption and amalgamation into the skeletal system. The main recommendation seems to be 600 IU of vitamin D per day until the age of 70, and 800 IU per day after the age of 70 (Pludowski *et al.*, 2018); however, some people may require more to achieve adequate blood vitamin D levels. It is challenging to obtain the correct levels of vitamin D from daily nutrition, and a vitamin D supplement may be needed in order to meet these requirements (Komoroski *et al.*, 2014). A study also stated that potassium enhanced calcium homeostasis; adults in general require 4,700 mg per day, but the majority fall short. This mineral can be found in various vegetables, including bananas, potatoes, prunes, orange juice, tomato juice, dried fruit, acorn squash, green beans, and spinach (Minich, 2019). Bone consists of polypeptide chains interlocked to mineral deposits with calcium connected. Protein is essential for bone strength and has been shown to aid in bone healing in some research (Herford, 2017). Reducing the excessive consumption of caffeine and alcohol can decrease bone mass. Tobacco use causes substantial bone resorption in both males and females and relatively long curing instances after a fracture, with an increased long-term complication. Quitting tobacco can help to reduce the additional risk (Kanis *et al.*, 2019).

MBD treatments are being developed, but it is more than 40 years since the first MBD medication was endorsed, with scientific understanding having progressed and safety issues having emerged that necessitate analysis of MBDs manifestations. Bisphosphonates very quickly became the benchmark for the treatment of MBDs since the mid-1990s and have become the most extensively used product class (Barbosa *et al.*, 2020). The EMA and FDA have endorsed numerous bisphosphonates for the treatment of all MBDs. Raloxifene,

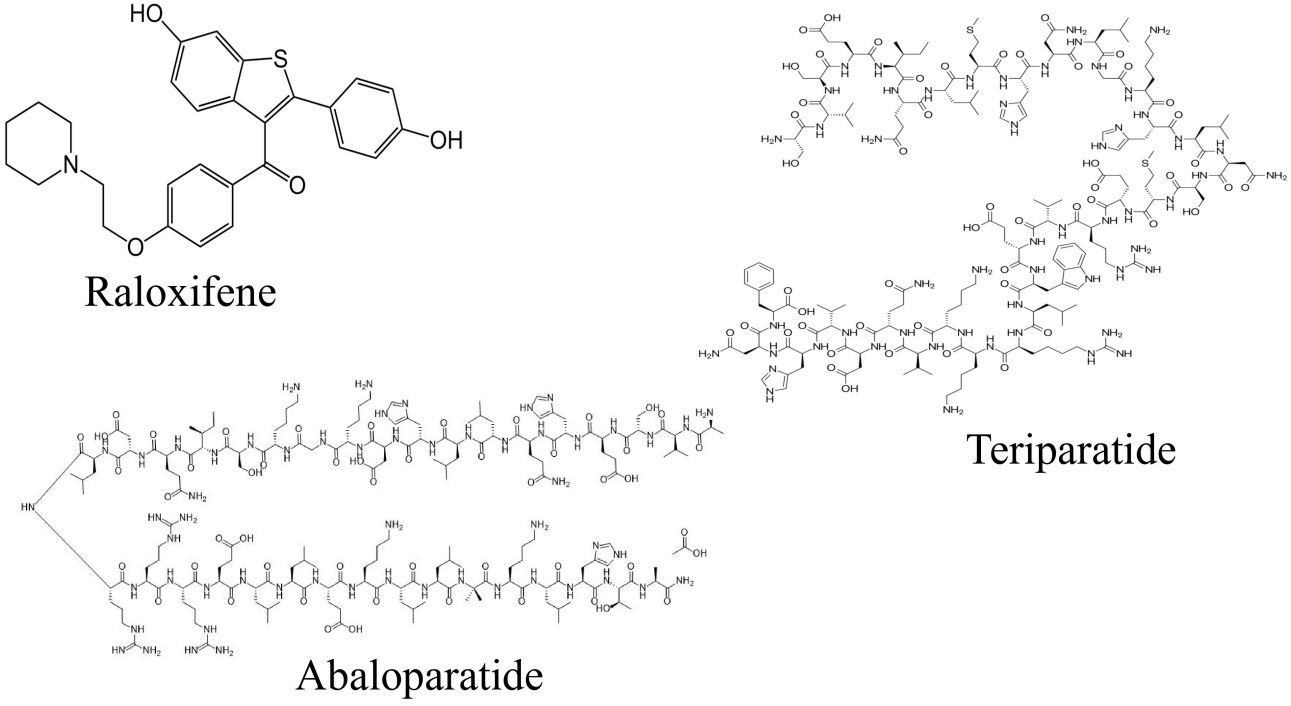

Fig. 6. Chemical Structure of Raloxifene, Teriparatide and Abaloparatide.

Table 1. Current monoclonal antibody drugs

Name of Monoclonal Antibodies	Uses
Denosumab	The first monoclonal antibody authorized to treat osteoporosis, Effective in reducing fracture risk (Moen and Keam, 2011).
Abciximab	Myocardial infarction (Stoffer *et al.*, 2022).
Basiliximab	It is used to prevent white blood cells from acute renal transplantation rejection (Kapic *et al.*, 2004).
Belimumab	Treats systemic lupus erythematosus (Dubey *et al.*, 2011).
Tocilizumab	It is prescribed to treat moderate to severe active arthritis, recently tocilizumab has been used to treat patients with COVID-19 (Samaee *et al.*, 2020).
Romosozumab	To treat osteoporosis in postmenopausal women at high risk of fracture (Lim and Bolster, 2017).
Secukinumab	Treats metastatic breast cancer (Berg *et al.*, 2021).
Golimumab	Used for the treatment of rheumatoid arthritis (Pelechas *et al.*, 2019).
Infliximab	It is used for Crohn's disease patients with intestine inflammation (Guo *et al.*, 2013).
trastuzumab	Breast cancer-inhibits the proliferation of tumour cells that overexpress HER2 (McKeage and Perry, 2002).

This table shows a list of monoclonal antibody-based drugs including those against metabolic bone diseases.

the first specific estrogen receptor stimulator for MBDs, became popular in the United States in 1997 and in the European Union in 1998 (Ott and Elder, 2021), while several novel treatments have emerged since the year 2000. Teriparatide, a small peptide chosen to represent the amino terminal fraction of human parathyroid hormone (PTH) and dealing as an agonist just at the PTH1 binding site, was accepted as a possible novel osteoanabolic treatment within the EU, as well as the US, in 2003 (Jiang *et al.*, 2020). In 2017, another osteoanabolic medicine, abaloparatide, was approved by the US FDA. The chemical structures of raloxifene, teriparatide and abaloparatide are shown in Fig. 6.

Recently found osseous metabolic activity and signaling pathways contributed to the growth of denosumab, the first monoclonal antibody to treat osteoporosis, which was authorized in 2010 (Jiang *et al.*, 2020), while the revelation of another signaling pathway significant in bone metabolism resulted in the emergence of romosozumab, a monoclonal antibody against sclerostin that has been studied in phase 3 trials and requires submission for regulatory approval (Fabre *et al.*, 2020). Meanwhile, the progress of odanacatib, a cathepsin K inhibitor, was recently halted at the sophisticated confirmative clinical trials stage (Table 1). Calcitonin is a nasal spray used to reduce spinal fractures by 25%; however, there is no proof that this reduces the risk of other fractures. Moreover, this is one of the well-tolerated MBD osteoporosis treatments (Albahri *et al.*, 2021). There are some concerning issues about even a potential 1% elevated risk with such a drug, and this has led to further evaluation by the FDA, which has enabled the drug to remain on the market by suggesting that the patient and physician discuss the risks and benefits. Raloxifene is a once-daily pill that has been used to reduce spine fractures by 30%. This can inhibit estrogen activity in bone tissues while enhancing other hormonal activity and reducing the risk of breast cancer, but it can still induce hot flashes and increase the risk of blood clots (Tu *et al.*, 2018).

Bisphosphonates can minimize the chances of spinal fractures by 50% to 60% and hip fractures by 50%. These medicines are prescribed as a once-daily or monthly pill, as well as a once-a-year intravenous injection (Carbone *et al.*, 2020).

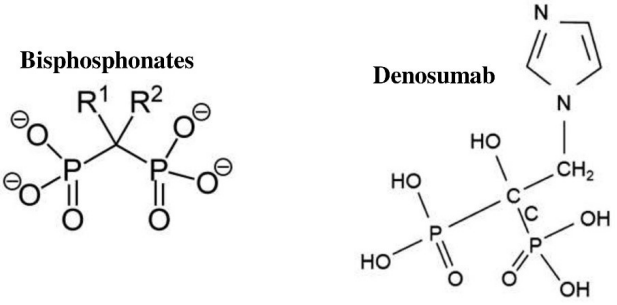

Fig. 7. Chemical Structure of Bisphosphonates and Denosumab.

Also with oral medications, side effects encompass small bowel side effects such as nausea and common cold manifestations during the first injection of intravenous treatments. There are also uncommon risks, such as poor healing after dental treatment. The chemical structure of bisphosphonates is shown in Fig. 7, along with denosumab, which is administered through subcutaneous injection twice per year and has been shown to decrease the risk of spine fractures by 50% to 60% and hip fractures by 50%. The FDA approved this as a medicine in 2010 (Izumiyama *et al.*, 2020).

Skin reactions, such as skin problems or dermatitis, are potential side effects and an elevated infection risk. Parathyroid hormone is administered once-daily by sub-cutaneous injection and has been shown to minimize the chances of bone fracture and thyroid disease by 65% and the risk of other broken bones by 53% (Cusano *et al.*, 2013). This medicine enhances bone remodeling instead of simply delaying bone breakdown. Skin reactions at the injection site, calcium levels rising in the blood and urine, and bone pain are possible side effects. In rats, high quantities of this medicine cause osteosarcoma, a type of bone cancer, but this has not been observed in humans (Cusano *et al.*, 2013). Testosterone administration also significantly increases bone density in those who possess a low level of this hormone (Soyka *et al.*, 2000). Denosumab is a drug formulated as an injection form to be

given to both males and females every six months and is frequently used after other treatment options have been refused. It can even be with an impaired kidney function (Soyka *et al.*, 2000). However, its long-term consequences are unknown, and there could be adverse health effects, including the possibility of thigh or jawbone problems, as well as severe infection.

Anabolic agents help to build bone in osteoporosis patients. Presently, three such drugs have been approved: romososumab has been recommended to treat post-menopausal women who may be at risk of MBDs (Laroche *et al.*, 2020), as the drug can promote bone regeneration and reduce bone fractures; meanwhile teriparatide and abaloparatide are intravenous parathyroid hormone drugs administered once a day for two years (Anagnostis *et al.*, 2019) and are comparable to the hormones in several aspects.

PROBLEMS AND SIGNIFICANT IMPROVEMENTS IN DRUG THERAPY

Bisphosphonates have been used as an antiresorptive treatment for the past three decades and are most commonly used for certain metabolic disorders (Abrahamsen *et al.*, 2012). Unfortunately, intravenous bisphosphonates cause a variety of side effects, including typical femur fractures, esophageal cancer, and jaw osteonecrosis (Reyes *et al.*, 2016). Surprisingly, significant formulation-based advancements have been made in bisphosphonates for oral administration to cure metabolic disorders. Fortunately, oral administration significantly reduces adverse effects, such as esophageal cancer and mortality due to adverse effects (Skjødt *et al.*, 2019). Tamoxifen is a popular drug to treat a variety of MBDs, including osteoporosis, but it can also have some negative side effects, such as increasing the risk of uterine cancer (Yang *et al.*, 2013). Hence, the alternative drug raloxifene was discovered to significantly reduce the risk of uterine cancer when used in place of tamoxifen (Provinciali *et al.*, 2016). Another well-known drug is teriparatide, which is a recombinant human-parathyroid hormone used to treat postmenopausal osteoporosis (Lombardi *et al.*, 2020). However, prolonged use of this drug significantly increases the risk of osteosarcoma, nausea, headache, arthralgia, hypercalcemia, and leg cramps (Tuli *et al.*, 2020). Another drug, romosozumab, was developed to replace the alendronate and teriparatide drugs in the treatment of MBD; however, severe cardiovascular events were observed in the second and third clinical trial phases (Kaveh *et al.*, 2020). Meanwhile, several Cat-K inhibitors are currently being studied in clinical trials for the treatment of osteomalacia, osteoporosis, and MBDs (Lu *et al.*, 2018). Odanacatib, an extremely selective and recoverable Cat-K inhibitor, is currently in phase 3 trials (Xue *et al.*, 2019). In phase II clinical trials, it reduced bone resorption, while only temporarily inhibiting bone formation, and its use for five years resulted in significant sequential increases in bone density at the hip and spine (Lu *et al.*, 2018). Different inhibitors are also being developed to treat MBDs with fewer side effects.

CONCLUSION AND FUTURE PERSPECTIVES

MBDs are virtually controllable with earlier detection and a focus on maintaining healthy nutritional habits. Around the world, the most common MBDs are found to be osteoporosis, PHPT, osteomalacia, and fluorosis disease. Aside from a nutritious diet, a balanced periodical supplementation of calcium, phosphate, and vitamin D can improve reabsorption and the regrowth of bones, and inhibit the formation of skeletal fractures, except in the case of hereditary bone diseases. A few drugs, including raloxifene, teriparatide, sclerostin, denosumab, romososumab, and abaloparatide, have been successfully developed and administered as treatments for people suffering from MBDs. However, some adverse effects are reported for most of the drugs used to cure MBDs. Researchers are still looking for more suitable medications, and this review suggests that individuals should gain an increased awareness of MBDs. Hence, it is important to find ADME (absorption, distribution, metabolism, and excretion) based research that can facilitate the effective treatment of various MBDs, with less adverse effect. Advanced bone-targeted nanosystem-related research for MBDs, as well as bone regeneration will soon be effective. Therefore, it is essential to enhance the implementation of effective therapeutic doses toward the bone disease site, while avoiding poisonous levels in the blood. Regional drug delivery systems seem to be an active research area for bone disorders. Nanoparticles can be used as carriers and should have a specific attraction for bone inorganic materials but should always be capable of targeting the site of the metabolic bone disorder and prolonging drug delivery. Moreover, the morphological characteristics of nanoparticles might be enhanced by physical and chemical adsorbents, to optimize nanocarriers for particular purposes. Various peptides can be attributed to the adsorption, helping to promote osteoblast capabilities, while rising claims indicate that they may also have a significant influence on transit to the bone.

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