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Metabolism and Target Organ Damage

Review

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Clinical frontiers of metabolic bone disorders: a comprehensive review

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Abstract

Metabolic bone disease (MBD)encompasses various conditions that adversely impact bone health, such as osteoporosis, primary hyperparathyroidism, osteomalacia, and fluorosis disease. Effectively managing these disorders requires early detection and a focus on maintaining healthy nutritional habits. Dietary adjustments serve as a cornerstone, but supplementation of essential minerals like calcium, phosphate, and vitamin D is often necessary to support bone reabsorption and regeneration, and reduce fracture risk. Despite the effectiveness of these measures in many cases, hereditary bone diseases pose distinctive challenges due to genetic factors. Emerging technologies that provide higher-resolution insights into bone architecture and quality are now complementing traditional diagnostic tools like dual-energy X-ray absorptiometry (DXA). Moreover, the therapeutic landscape has transformed with the introduction of newer agents that not only halt bone loss but also stimulate bone formation. These agents promise better outcomes with reduced side effects, catering to a wider patient population. However, the management of MBDs remains multifaceted, necessitating individualized approaches based on the patient's clinical profile. As the global prevalence of MBDs, especially osteoporosis, continues to soar, it becomes imperative for clinicians to stay abreast with the evolving paradigms. This review serves as a bridge between historical knowledge and recent discoveries, offering a holistic perspective on the challenges and opportunities in the domain of MBDs.

Keywords: MBDs, osteoporosis, osteomalacia, fluorosis, hyperparathyroidism, treatments

INTRODUCTION

Different metabolic bone disorders (MBDs) weaken the skeleton by damaging individual bones or compromising the bone matrix. The intricate balance between bone development, bone degradation, and mineralization is disrupted in several diseases. This causes skeletal pain, frailty, and bony deformities, as well as an increased likelihood of fractures in people with these disorders[1]. In the body, hormones, minerals, and other substances stimulate bone tissue to adapt to the environment. Disruption of these control mechanisms has been linked to the development of MBD through poor diet, hormonal imbalance, heredity, and certain drugs[2]. In many cases, the symptoms and signs of MBD may be reversed by treating the underlying cause of the condition. Disruptions in the systems that govern mineral homeostasis led to abnormally high or low quantities of minerals, including calcium, phosphorus, magnesium, or vitamin D. Rickets in the growth plates and osteomalacia of the inner cortical and trabecular bone surfaces are also possible outcomes of inadequate mineralization [Figure 1]. The causes of Osteogenesis Imperfecta (OI) have been widened beyond their original emphasis on a flaw in collagen to encompass anomalies in bone cell metabolism and maturation, with particular attention paid to conditions in the differentiation of osteoblasts[3]. Distinct from MBD, the hereditary disorders known as skeletal dysplasia are characterized by systemic abnormalities in the skeletal framework. Different bone disorders may be traced back to specific malfunctions in the signaling pathways or cell types responsible for regulating skeletal development. Forensic pathologists face a difficult diagnostic conundrum when a newborn presents with many unexplained fractures since it is difficult to tell the difference between child abuse and MBD in such circumstances[2].

Accurate diagnosis, efficient treatment, and the avoidance of subsequent difficulties all depend on a thorough understanding of the many kinds of MBDs, their underlying causes, and their clinical repercussions. This review of MBD focuses on the complicated nature of these conditions, emphasizing their implications for bone health and the challenges they pose to both patients and medical professionals[4].

CLASSIFICATION OF MBD

Osteoporosis

Definition

Osteoporosis is a common bone disease that causes bones to become fragile and increases the likelihood of breaking. This condition causes a loss of bone density and quality, which increases the risk of fracture and bone fragility. Reduced bone mass and structural integrity result when the rate of bone breakdown exceeds that of bone production[5]. Therefore, even minor incidents or falls may cause fractures, the most common sites of which are the spine, hips, upper humerus, and wrists. Despite its common moniker as the "silent disease," osteoporosis often worsens without warning until a fracture occurs, highlighting the critical need for early diagnosis and treatment for successful management[6].

Epidemiology

An osteoporotic fracture occurs every three seconds on average, accounting for 8.9 million fractures annually throughout the globe. Nearly 6.3% of people aged 50 and older are afflicted by this disorder worldwide, with women having a higher risk than men at 21.2%[7]. These estimates suggest that over 500 million men and women throughout the world are affected. Osteoporosis affects 82 million individuals in Europe, the United States, and Japan. Approximately 9 million osteoporotic fractures were recorded in the year 2000[8]. This number includes 1.6 million hip fractures, 1.7 million forearm fractures, and 1.4 million clinical vertebral fractures. About half of all fragility fractures occur in Europe and the United States, with the rest occurring largely in the Western Pacific and Southeast Asia[9]. Hip fractures are expected to grow

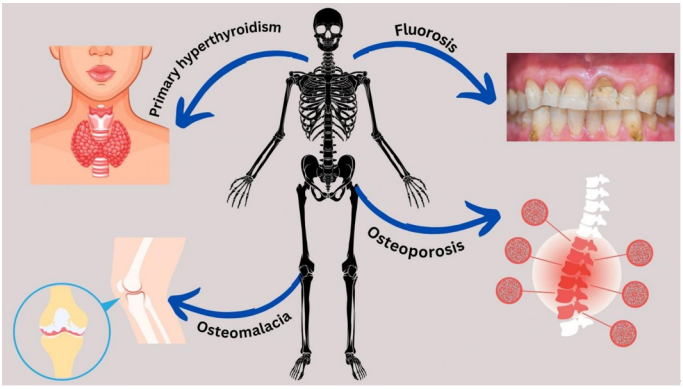

Figure 1. The most prevalent MBDs are osteomalacia, osteoporosis, primary hyperthyroidism, and fluorosis, caused by imbalances in key minerals including Ca, P, and vitamin D, leading to bone mass and structure loss. MBDs: metabolic bone disorders.

worldwide from 1990 levels by 310% for men and 240% for women by 2050[10]. Due to population shifts, the number of people at risk of osteoporosis is projected to more than double by 2040, from an estimated 158 million in 2010[11]. Osteoporotic fractures affect one in three women and one in five men over the age of 50[5,12]. Forearm, humerus, hip, and spine fractures are more common in women than in males[13], and women also make up 61% of all osteoporotic fractures. Fractures of the hip, spine, and distal arm account for over 75% of all fractures in patients aged 65 and older. When bone density in the hips or spine decreases by 10%, the risk of fracture increases by 2.5 times, and when bone density in the spine decreases by 10%, the risk of fracture doubles. Hip, forearm, and spine fractures that need medical treatment have a lifetime risk of around 40%, which is higher than the chance of developing cardiovascular disease[14].

Risk factors

Osteoporosis, which refers to "porous bone", is a medical illness in which the bones' interior structure weakens to the point that a fracture may occur from a very modest fall or impact[15]. While every bone in the body is susceptible to breaking, the wrists, hips, and spine are especially at risk. However, a network of specialized cells constantly renews the microscopic collagen structure, and minerals like calcium help to maintain bone health over a lifetime[16]. The process by which worn-out bones are replaced by new bones occurs periodically in the body. Bone density increases as long as this process is in equilibrium, a phase that generally persists until around age 25[17]. Between the ages of 25 and 50, both bone growth and resorption occur at about the same pace, keeping bone mass relatively constant. Bone loss accelerates after menopause and often outpaces bone production beyond age 50. Women are at greater risk than men because their bones tend to be thinner and less thick. A decline in estrogen levels, such as during menstruation, further heightens the risk, as estrogen plays a pivotal role in bone development. The likelihood of developing osteoporosis is elevated in both genders when there is a familial record of fractures attributed to the condition[18].

Pathophysiology

Osteoporosis disrupts bone remodeling, a continuous process where osteoclasts (cells that break down bone) and osteoblasts (cells that form bone) work in parallel. Changes in hormone levels, age, inflammation, genetics, and even lifestyle choices may all contribute to this discord. Factors such as the reduction in estrogen levels after menopause, which speeds up the rate of bone resorption, contribute to the imbalance that leads to osteoporosis. Age-related decreases in osteoblast activity also contribute to the disorder[19]. Bone loss and bone growth may be accelerated and inhibited, respectively, by cytokine-mediated pathways in conditions where chronic inflammation is prevalent, such as in rheumatoid arthritis. Genetic factors,

particularly variants in specific genes, may have an impact on bone density and turnover. A sedentary lifestyle, smoking, and binge drinking are some factors that exacerbate bone fragility[7].

Bones become more porous and brittle, increasing the risk of fractures, particularly in weight-bearing areas such as the spine, hips, and wrists. These fractures have devastating clinical consequences, lowering quality of life, and even shortening life expectancy, especially in the older population. To reduce the burden of osteoporosis on both patients and healthcare systems, it is essential to get a deeper understanding of the complicated biology behind this remodeling imbalance in bone[20].

Clinical manifestations and diagnostic tools

Fractures are the most devastating complication of osteoporosis; however, the disease may manifest with a wide spectrum of clinical signs. In its early stages, the condition is often asymptomatic, although some people may notice a loss of height and the development of a hunched posture due to vertebral fractures. Fractures may occur from quite small injuries. Hip fractures are particularly concerning since they pose serious health hazards and significantly restrict a person's mobility[4]. Even mild falls might cause a fractured wrist. Osteoporosis may be diagnosed, and the risk of fractures may be assessed using several different techniques[4].

T-scores, which compare an individual's BMD to that of a healthy young adult, aid in the diagnosis of osteoporosis using dual-energy X-ray absorptiometry (DEXA), the gold standard for determining bone mineral density (BMD).

Biochemical markers of bone metabolism, such as serum osteocalcin and C-terminal telopeptide levels, can also be used to measure bone remodeling[21]. In addition, secondary osteoporosis should be excluded by following laboratory tests: sedimentation rate (SR), blood count, alkaline phosphatase (ALP), ionized calcium, creatinine, serum 25-hydroxyvitamin D (S-25OHD), transglutaminase antibodies, thyroid-stimulating hormone (TSH), and testosterone in men[22].

Improved fracture risk estimates may be achieved with the use of modern imaging techniques like quantitative computed tomography (QCT), which provides three-dimensional assessments of bone density[23]. The FRAX tool is one example of a risk assessment instrument that uses a combination of risk variables to predict a person's 10-year risk of major osteoporotic fractures[18]. These diagnostic tools work together to improve osteoporosis care by allowing for earlier detection, more accurate risk assessment, and treatment based on solid scientific data.

Current treatment strategies and challenges

Treatments for osteoporosis today are aimed at restoring normal bone remodeling, boosting bone density, and decreasing the likelihood of fractures. In this model of care, pharmaceutical medicines play a significant role. Bone-resorbing cells (osteoclasts) may be slowed with the use of bisphosphonates like risedronate, ibandronate, alendronate, and zoledronic acid[24]. Hormone replacement therapy (HRT) and other agents with estrogen-like properties, such as the selective estrogen receptor modulator (SERM) raloxifene, are effective against bone loss[25]. Antibodies like denosumab stop bone loss by going after receptor activators of nuclear factor kappa B ligand (RANKL), which is a protein that osteoclasts need to grow. Teriparatide is an anabolic steroid that increases bone density and strength[26].

Long-term commitment, possible side effects, and the intricacy of regimens all contribute to less-than-ideal drug compliance. Given that prolonged usage may occasionally lead to uncommon but significant adverse

effects such as osteonecrosis and atypical femoral fractures, the optimum length for several therapies is still up for dispute. It is challenging to determine who is at the highest risk for fractures since so many fractures occur in people with no known risk factors. Effective osteoporosis management also involves preventative efforts, such as modifying one's lifestyle and participating in programs designed to lessen the likelihood of experiencing a fall.

The potential exists in novel therapy approaches, such as sclerostin and cathepsin K inhibitors; however, this area needs additional research. There has been a recent trend towards tailoring medical care to each patient based on their unique set of circumstances [Figure 2]. While there have been improvements in the management of osteoporosis, more work needs to be done to improve patient outcomes and reduce the societal impact of osteoporotic fractures by increasing medication adherence, accurately identifying high-risk patients, and refining treatment options[27].

Rickets/osteomalacia

A severe deficiency of vitamin D is the primary cause of osteomalacia, a disorder characterized by bone weakening. Deformities, especially in the weight-bearing bones of the legs, may occur at a young age because of this softening[28]. In the elderly, this disorder can lead to fractures. In addition to treating any underlying disorders causing the illness, the primary treatment methods involve ensuring adequate intake of vitamin D and calcium to strengthen and harden bones[29].

Osteomalacia is increasing in prevalence around the world, in both high- and low-income regions. A lack of calcium can be the root cause of reduced bone mineralization (such as rickets and osteomalacia), seizures brought on by low calcium levels, muscle spasms, and even heart conditions that could lead to heart failure and death. The death rate from untreated osteomalacia in children is as high as 25%, yet the real scope of subclinical rickets and osteomalacia is still unknown[30].

The prevalence of vitamin D insufficiency in European populations during the colder months has been the subject of various studies. One notable study found that during winter months, the prevalence of vitamin D insufficiency is higher in European adults, with a reported rate of 39.3% compared to 25.0% in other seasons[31]. However, people of color had anything from a three- to seventy-one times increased risk[28]. Vitamin D insufficiency and osteomalacia are both on the rise, with people of color being disproportionately affected.

Causes of rickets/osteomalacia

Inadequate levels of minerals such as calcium and phosphate are the primary cause of osteomalacia. This disease may develop if these minerals are not ingested or absorbed effectively[32].

Fibroblast Growth Factor 23 (FGF23) plays a crucial role in the development of hypophosphatemia and osteomalacia. FGF23 is a hormone primarily produced by osteocytes and osteoblasts in bone, and it regulates phosphate and vitamin D metabolism[33]. FGF23 decreases serum phosphate levels by reducing phosphate reabsorption in the kidneys. It does this by downregulating the expression of sodium-phosphate cotransporters in the renal tubules, leading to increased phosphate excretion in urine. FGF23 also suppresses the synthesis of 1,25-dihydroxyvitamin D (the active form of vitamin D) in the kidneys[30]. It inhibits the enzyme 1α-hydroxylase, which is responsible for the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D. This reduction in active vitamin D levels further contributes to decreased intestinal absorption of phosphate[34]. Excessive levels of FGF23 result in hypophosphatemia, a condition characterized by abnormally low levels of phosphate in the blood. This can occur in certain genetic

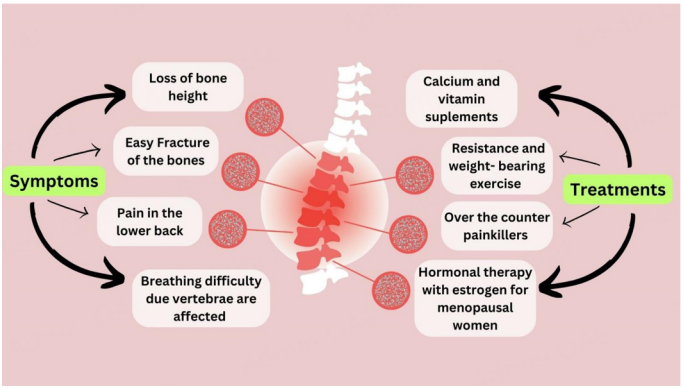

Figure 2. Symptoms and treatment of osteoporosis.

disorders, tumors, or as a side effect of certain medications[35]. Chronic hypophosphatemia can lead to osteomalacia, a condition where bones become soft and weak due to defective bone mineralization. In osteomalacia, the bone matrix is produced normally but is inadequately mineralized with calcium and phosphate. The role of FGF23 in causing hypophosphatemia directly contributes to the development of osteomalacia[28].

Vitamin D plays a vital role in the body's ability to absorb calcium, making its deficiency a significant concern. While many individuals obtain their vitamin D from enriched sources like cow's milk, the skin can also produce it upon exposure to sunlight. Osteomalacia is more common in those who do not get enough vitamin D from their diets or who live in places with minimal sunshine[36].

These vital minerals are typically released during digestion and absorbed in the intestines. Intestinal lining damage, such as that caused by gluten, may interfere with this absorption, leading to vitamin D and calcium deficiency. Disorders affecting kidney or liver function, along with certain drugs such as phenytoin and phenobarbital, may prevent the activation of vitamin D[32].

Therapeutic implications

The standard treatment involves administering oral phosphate salts and vitamin D metabolites or analogs multiple times a day. The typical phosphorus dosage varies from 20 to 40 mg/kg/day, distributed three to five times daily, while the calcitriol dosage typically ranges from 20 to 30 ng/kg/day. Treatment initiates with a low dose to minimize gastrointestinal side effects, gradually increasing until symptoms improve and serum phosphorus levels return to normal. This approach aids in resolving radiographic rickets and enhancing growth, although complete normalization of growth may not be achieved, and some patients may still require corrective surgery for deformities. As individuals reach adulthood, the necessity for treatment varies, with some not requiring it or only needing a low dose of calcitriol. However, prolonged conventional treatment with calcitriol and phosphorus can result in complications such as hypercalcemia, hypercalciuria, nephrolithiasis, nephrocalcinosis, impaired renal function, and the potential development of chronic kidney disease. Additionally, Burosumab, an antibody targeting FGF-23, has received approval from regulatory agencies as an innovative treatment for these conditions, offering an alternative to standard treatment[37,38].

Primary hyperparathyroidism

The symptoms of primary hyperparathyroidism (PHPT) include, but are not limited to, bone pain, fractures, and disorders with kidneys and gallstones. Those who are less likely to have symptoms[39]. Elevated

levels of intact parathyroid hormone (PTH) and calcium are observed in these patients, while phosphate levels are reduced. Certain mutations in the parathyroid adenoma's production of PTH or PTH-related peptide (PTHrP) can lead to low or even undetectable PTH levels[40].

The serious difficulties of PHPT make it difficult to decide whether to undergo surgery. Some of these include inflammation, kidney cysts, hypertension, and nephrocalcinosis; others include obesity, dehydration, insulin resistance, kidney tubule damage, kidney stone formation, chronic kidney disease, and an increase in cardiovascular risks[41]. Due to the wide range of symptoms and the risk of serious consequences, managing PHPT presents several difficulties.

Role of parathyroid hormone in bone health

PTH regulates calcium and phosphate levels, making it crucial for bone health. It is secreted by the parathyroid glands and functions to maintain a delicate balance between bone resorption and bone production, thereby facilitating bone remodeling[40].

Calcium and phosphate regulation

PTH primarily affects bone health by influencing serum calcium and phosphate levels. When blood calcium levels drop, the parathyroid glands secrete PTH. This hormone travels throughout the body and eventually reaches the bones, where it triggers osteoclasts to begin the process of bone resorption and release calcium into the blood. In addition to raising blood calcium levels, PTH also prevents calcium from being lost via the kidneys and increases the body's ability to reabsorb calcium[42].

Bone remodeling

PTH is an important link in the chain that connects bone breakdown and repair throughout the continuous cycle of remodeling. When blood calcium levels drop, PTH releases calcium from the bones into the bloodstream. This keeps the body’s supply of calcium constant. The calcium produced during bone resorption serves as a bridge until the body can absorb calcium from food. PTH also promotes the development and functional activation of osteoblasts, the cells primarily responsible for making new bone, further contributing to the bone production process. The structural integrity and mineral content of bones rely on a balance between bone breakdown and regeneration[43].

Vitamin D metabolism

PTH works closely with vitamin D to increase calcium absorption from the intestines. This enzyme in the kidneys transforms vitamin D from its inactive form, calcidiol, into its active variant, calcitriol. The activation of vitamin D3 promotes the absorption of calcium and phosphate in the digestive system, subsequently supporting bone health[29].

Clinical significance

Changes in PTH levels can significantly affect bone health. Excessive secretion of PTH, known as hyperparathyroidism, can lead to bone weakening and a heightened fracture risk. On the other hand, hypoparathyroidism, where PTH production is insufficient, can lead to reduced blood calcium levels. This deficiency might lead to symptoms such as muscle cramps, seizures, and compromised bone mineralization[42].

Therapeutic implications

Understanding the role of PTH in bone maintenance has led to the development of therapies that specifically target this process. Teriparatide, a synthetic form of PTH, is one such anabolic therapy routinely

recommended for severe osteoporosis. Furthermore, PTH receptor-interacting drugs like cinacalcet are used to control hyperparathyroidism and other conditions associated with elevated PTH levels[44].

Causes of PHPT

The parathyroid glands secrete hormones in response to low calcium levels in the body. In people with PHP, overactive glands cause this hormone discharge[39]. When PHPT and high parathyroid hormone levels coexist, hypercalcemia, which results from the constant release of parathyroid hormone, is a clinical sign[45]. Calcium plays a crucial role not only in bone formation but also in heart and muscle activity, blood clotting, muscular contractions, and nerve communication[41].

Adenomas are benign tumors responsible for the majority of PHPT cases. One or more of the four parathyroid glands may develop a benign tumor called an adenoma, which may cause the glands to become overactive. About 6%-12% of all instances of PHPT are multi-gland hyperplasia, which is caused by rapid cell proliferation[39]. Both sporadic and inherited forms of this are possible.

What causes adenomas to arise in the parathyroid glands is still not known. It has been suggested that genetic changes, either spontaneous or inherited, play a role in the onset of PHPT[46]. Rarely affecting only one gland, inherited variants of PHPT account for around 10% of all cases. Mutations in the MEN1, CDC73, and CASR genes have been linked to the disorder[47].

Less than one percent of all instances of PHPT are attributable to the thyroid. Although there are contradictory data supporting radiation therapy for hyperthyroidism, radiation exposure, particularly in early life, is considered a risk factor for PHPT. Commonly used to treat bipolar illness, lithium has been linked to hypercalcemia in roughly 25% of patients[47]. It is expected that other genetic variables and the interaction between them will be discovered in future studies[48].

Fluorosis

Fluoride is a toxic substance that accumulates in the body and affects both the formation and breakdown of bone tissue, impacting bone mineral metabolism or homeostasis. The total amount of fluoride consumed has a significant impact on the disease's severity, which is characterized by the immobilization of the spinal and major limb joints[49]. The primary source of fluorosis is fluoride-contaminated drinking water, which becomes hazardous to health when concentrations exceed 1.5 mg/L; the alkaline pH of water makes fluoride absorption easier, whereas the presence of calcium can lessen fluoride's toxic effects[50].

Fluorosis leads to hormonal alterations essential for the metabolism of bone minerals. The kidneys serve as the primary organ for fluoride removal from the body[51]. Several factors influence the severity and outcome of fluorosis, including age, gender, calcium intake, duration and level of fluoride exposure, and the efficiency of the kidney and liver in processing fluoride[52].

When fluoride builds up in the body to dangerous levels, however, a condition known as fluorosis may develop. Fluorosis may affect the teeth, bones, or other parts of the body. Skeletal fluorosis is more frequent in adults than dental fluorosis is in children. Non-skeletal fluorosis may affect people of any age after continuous exposure to high fluoride levels. Skeletal fluorosis affects millions of people, particularly in China and India[28].

Fluorosis can manifest as tooth staining and severe bone diseases, among other symptoms. People with skeletal fluorosis have also reported intense pain, rigidity in the joints, and, in some cases, paralysis due to

compression of the spine[53]. Excessive fluoride consumption has negative effects on several tissues, including skeletal muscles, red blood cells, and the digestive system. While osteomalacia and fluorosis both impact bone health, their effects, causes, and symptoms differ. Recognizing these distinctions can aid in the accurate diagnosis and treatment of these conditions.

Metabolic fatty liver syndromes

Metabolic-associated fatty liver disease (MAFLD), also referred to as metabolic fatty liver syndrome, is a condition where there is an excessive buildup of fat in the liver. This often occurs without the influence of heavy alcohol intake. It is closely linked with metabolic issues like obesity, resistance to insulin, type 2 diabetes, and abnormal lipid levels in the blood.

Non-alcoholic fatty liver disease

Non-Alcoholic Fatty Liver Disease (NAFLD) is a common liver ailment characterized by an excessive buildup of fat in the liver, even in those who drink minimal to no alcohol. The disease can range from a simple fatty liver to more advanced stages such as non-alcoholic steatohepatitis (NASH) and cirrhosis. Factors like obesity, insulin resistance, type 2 diabetes, and abnormal lipid levels contribute to its occurrence. With the rise in global obesity rates, the incidence of NAFLD has also grown. To diagnose it, doctors may use physical checks, imaging, and sometimes liver biopsies. The primary treatment is lifestyle modifications such as adopting a healthier diet and regular exercise. In advanced cases, medication or even liver transplantation may be necessary. It is vital to address NAFLD early and with a comprehensive approach to prevent further complications. Additionally, those with NAFLD have a heightened risk of lacking vitamin D. This deficiency can be due to factors like limited exposure to sunlight, being overweight, and decreased absorption of vitamins that dissolve in fat. Vitamin D plays a pivotal role in absorbing calcium and maintaining bone strength. A shortage can lead to fragile bones and a higher risk of bone diseases like osteoporosis[54,55]. Both NAFLD and metabolic bone conditions like osteoporosis share connections with insulin resistance and persistent mild inflammation. Insulin resistance can upset the equilibrium of bone turnover, leaning more towards bone breakdown than creation. Likewise, inflammation can adversely impact bone thickness[56,57]. Conversely, the hormonal shifts seen in NAFLD, such as changes in sex hormones and adipokines, could influence bone well-being. Hormones are vital in preserving bone thickness and overseeing the bone regeneration cycle[55]. Being overweight, often seen in NAFLD cases, is linked to metabolic bone issues. Carrying extra weight can place additional stress on bones, which might cause alterations in their structure and density. The liver is involved in creating specific proteins crucial for bone health. When the liver does not function properly due to NAFLD, it might disrupt the production of these proteins, affecting bone metabolism indirectly[54,58]. Liver issues arising from NAFLD might interfere with the production of proteins essential for bone health, thereby indirectly altering bone metabolism. Moreover, some drugs prescribed for NAFLD, such as glucocorticoids, can negatively impact bone well-being. On a brighter note, the lifestyle changes suggested for NAFLD, including shedding weight and engaging in physical activity, can beneficially affect bone density[59,60].

Metabolic dysfunction associated fatty liver

MAFLD is a concern for nearly one-third of people worldwide. Its prevalence has risen alongside the increasing occurrences of type 2 diabetes and obesity. MAFLD enhances the chances of advanced liver disease, liver cancer, mortality, and the need for liver transplantation. Additionally, it can lead to non-liver-related issues such as metabolic disorders and other types of cancers. Even though it is commonly linked to obesity, evidence suggests that not everyone who is overweight or obese will face fatty liver disease. Conversely, many MAFLD patients have a normal weight, highlighting that metabolic health plays a significant role in the disease's onset, regardless of one's weight. The specifics regarding "lean MAFLD" patients, including their clinical features, progression, and underlying mechanisms, remain inadequately

understood[61]. Several factors elevate the risk of vitamin D deficiency in patients, such as limited sunlight exposure (essential for vitamin D production), being overweight (which can trap vitamin D in fat cells), and decreased absorption of vitamins that dissolve in fat. Vitamin D is vital for absorbing calcium and ensuring bone health. A shortage of this vitamin can result in fragile bones[62].

Metabolic dysfunction-associated steatotic liver

Metabolic dysfunction-associated steatotic liver, commonly known as MAFLD, is a condition where there is an undue buildup of fat (steatosis) in the liver due to metabolic issues. This name underscores the intertwined relationship between metabolic irregularities and liver fat accumulation[63]. The connection between metabolic dysfunction-associated steatotic liver and bone conditions is a burgeoning field of study. The exact reasons and causal relationships behind this link are not completely clear yet, but there are various indicators pointing towards a possible relationship between MAFLD and the health of bones[64].

PREVENTION, POSSIBLE TREATMENT, AND DRUG DEVELOPMENT FOR MBDS

Preventing MBDs requires taking measures to preserve bone mineral density. Getting enough calcium in your diet might reduce your chances of breaking a bone. Although some studies have cast doubt on whether calcium supplements cause vascular calcification, the vast majority of studies back using them regularly[65] provide recommendations that women between the ages of 50 and 70 and males over the age of 70 take 1,000 mg per day. Calcium-rich foods like low-fat dairy and leafy greens also supply protein and magnesium[66]. Those who are unable to get enough calcium in their diet may benefit from taking a supplement[67].

Calcium absorption is impaired without enough vitamin D; therefore, it is important to get the recommended amount of 600 international units (IU) per day before age 70 and 800 IU thereafter[68]. According to the Nordic Nutrition recommendations, adult females and males should use vitamin D as follows: 10 μg/day (≥ 75 years: 20 μg/day). For people with little or no sun exposure, an intake of 20 μg/d is recommended[69]. The Nordic and Baltic countries are situated at latitudes (54-71°N) where the sun radiation is insufficient for part of the year for vitamin D3 production in the skin to occur. Food sources of vitamin D3 are fish, especially fatty fish like salmon, trout, mackerel, herring, and egg yolk. Some products (including milk, butter, and margarine) are fortified to varying degrees in most of the Nordic countries[70]. To prevent osteoporosis and improve survival after osteoporotic hip fracture by means of nutrition, interesting findings regarding the improvement of vitamin D concentrations at the population level have been published[71]. Getting enough vitamin D from diet alone may be challenging; therefore, many people turn to pills instead. Even though potassium aids in calcium homeostasis, few individuals consume the recommended 4,700 milligrams per day[72]. Protein's involvement in bone repair has been the subject of research. Bisphosphonates have been the standard in treating bone loss. Raloxifene and teriparatide are only two examples of the many drugs that have been approved for the treatment of MBDs[73]. New therapeutic options are becoming available with the introduction of drugs such as denosumab[26]. There are advantages and disadvantages to using other medications, such as calcitonin and parathyroid hormone[2].

Different medications have different benefits and downsides, including different side effects and variable degrees of effectiveness in lowering the risk of fractures. Those with low hormone levels may benefit greatly from some therapies, such as testosterone therapy. Newly approved medications for the treatment of osteoporosis include anabolic agents, which stimulate bone growth[74]. Given the variety of treatment choices and the associated dangers, it is crucial for doctors and patients to carefully assess the pros and cons.

CONDITIONS AND SIGNIFICANT IMPROVEMENTS IN DRUG THERAPY

Antiresorptive therapies, such as bisphosphonates, are often used in the management of MBDs such as osteoporosis. Although they have been widely used for decades, there are serious risks associated with intravenous administration, including the development of rare fractures, esophageal malignancy, and jawbone necrosis. The use of oral bisphosphonates appears to lessen some of these risks, such as esophageal cancer and death from side effects[18].

Tamoxifen, another medicine often used for MBDs, has the drawback of raising the risk of uterine cancer. In response, raloxifene was launched, and it proved to be much more effective than tamoxifen in preventing uterine cancer[75].

Teriparatide is another option for treating osteoporosis after menopause. It is a synthetic form of human parathyroid hormone. Although beneficial, there are certain risks associated with using it for a lengthy period. To combat the limitations of alendronate and teriparatide, romosozumab was created for postmenopausal women. Phase 2 and 3 clinical studies of this medicine, however, uncovered major cardiovascular concerns[73].

Cathepsin K (Cat-K) inhibitors are also the subject of current research for the treatment of MBDs such as osteomalacia, osteoporosis, and others. Drugs that increase bone density without considerably reducing bone production are desperately needed, and the current phase III studies of odanacatib have shown encouraging results. It is the goal of the many different inhibitors now in development to provide effective therapy with minimal adverse effects[76,77].

SUMMARY

The main findings of the review were various MBDs, including osteoporosis, osteomalacia, fluorosis, and primary hyperparathyroidism. It emphasizes the importance of early detection and maintaining healthy nutritional habits in managing these disorders. The review highlights the role of dietary adjustments and supplementation with essential minerals such as calcium, phosphate, and vitamin D in supporting bone reabsorption and regeneration, and reducing fracture risk. Emerging technologies provide higher-resolution insights into bone architecture and quality, complementing traditional diagnostic tools like dual-energy X-ray absorptiometry (DXA) and the introduction of newer therapeutic agents that not only halt bone loss but also stimulate bone formation, offering better outcomes with reduced side effects. The management of MBDs is multifaceted, necessitating individualized approaches based on the patient's clinical profile. The global prevalence of MBDs, especially osteoporosis, is increasing, which underscores the need for clinicians to stay updated with evolving paradigms in the field and aims to bridge historical knowledge and recent discoveries, offering a comprehensive perspective on the challenges and opportunities in the domain of MBDs along with tailored treatment strategies based on the unique clinical profiles of patients suffering from MBDs.

The possible limitations of this review were a subjective interpretation of data and literature as the field of metabolic bone disorders is rapidly evolving. Additionally, this review did not sufficiently address how socioeconomic and cultural factors influence the management and treatment of metabolic bone disorders, which is crucial for understanding patient adherence and treatment efficacy in diverse populations.

CONCLUSION AND FUTURE PERSPECTIVES

MBDs have a serious influence on a person's bone health, and effective treatment of these conditions requires both early detection and the maintenance of appropriate dietary habits. Adopting a healthy diet is a

vital strategy for controlling MBDs. Dietary changes may support bone reabsorption, regeneration, and a reduction in the risk of skeletal fractures; however, regular supplementation with crucial minerals such as calcium, phosphate, and vitamin D can further promote these processes. Except for hereditary bone illnesses, where genetic factors play a key role, these interventions are beneficial in most instances.

Several medications have been created to treat MBDs, giving patients new reasons for optimism. Abaloparatide, denosumab, romosozumab, teriparatide, raloxifene, and sclerostin inhibitors are all examples of such drugs. Drugs for these conditions have shown promise in treatment, but it is crucial to remember that they also carry the risk of side effects. Efforts to find better medicines that can treat people effectively with fewer adverse effects are continuing. As a result, there is an increasing interest in studying these medications to enable more effective and tailored therapy for a wide range of MBDs. The objective is to reduce the potential for hazardous levels in the circulation while simultaneously improving the targeted delivery of therapeutic dosages to the location of the bone disease.

Future research should aim to include a more diverse range of participants in terms of age, gender, ethnicity, and geographical location to enhance the generalizability of findings. There is a need for long-term, longitudinal studies to better understand the progression of MBDs over time and the long-term efficacy and safety of various treatment strategies. Additionally, there is a need to understand how socioeconomic status and cultural factors influence the management, treatment, and patient compliance in MBDs. This can aid in developing tailored interventions. Incorporating patient-reported outcomes and experiences in research can provide a better understanding of the real-world impact of MBD treatments.

DECLARATIONS

Authors' contributions

Contributions to conceptualization and project administration: Sultana Y, Khan A
Contribution to investigation, methodology, data curation, and writing: Ansari MD, Majid H

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Conflict of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate.

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Consent for publication

Not applicable.

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