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Original Article

Osteoporosis a multi-faculty disorder: Going beyond the horizon

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ABSTRACT

Osteoporosis is a complex disease that is characterized by a reduction in bone mass and strength, resulting in weakened bones and an increased risk of fractures. Women are more susceptible to osteoporosis, particularly postmenopausal women due to the decline in estrogen levels. Risk factors for osteoporosis include age, genetics, lifestyle factors such as physical inactivity, and certain medical conditions. At the molecular level, osteoporosis is initiated by an imbalance between bone resorption and formation, mediated by various cytokines and mediators. This review comprehensively examines the multi-faceted nature of osteoporosis and its coexistence with other medical conditions, such as diabetes, chronic kidney disease, and menopause. The review highlights the need for a multidisciplinary approach to the management of osteoporosis in patients with comorbidities, including proper fracture management, evaluation of reversible risk factors, and appropriate follow-up plans. Furthermore, nutrition plays a crucial role in the management of osteoporosis, and routine nutritional assessments should be conducted to combat malnutrition, particularly in patients with fragility fractures. The review concludes that early detection and screening for osteoporosis in patients with coexisting medical conditions is crucial to prevent further complications and reduce the long-term impact on bone health and overall health outcomes.

Keywords: osteoporosis, diabetes mellitus, multidisciplinary approach

INTRODUCTION

Osteoporosis is a systemic disease characterized by the complex and multifactorial interplay of molecular pathways that reduce bone mass and strength, accompanied by microarchitectural degradation of bone. A major consequence of osteoporosis is a decrease in bone mineral density (BMD), which is strongly associated with an increased risk of fractures and weakened bones. Although osteoporosis and its adverse outcomes, such as fractures and chronic pain, can occur in both genders, women are known to be more susceptible, accounting for a substantial majority (70-80%) of all fractures, including those affecting the hip, spine, and wrist. This increased vulnerability is further exacerbated in postmenopausal women due to the decline in estrogen levels, which accelerates the loss of bone mass.[1]

According to data from the World Health Organization (WHO), osteoporosis affects approximately 30% of postmenopausal women globally. In India, a staggering 61 million individuals are diagnosed with osteoporosis, with women constituting 80% of the cases. Notably, the incidence of osteoporosis peaks earlier by 10-20 years in India compared to Western countries, posing significant health and economic challenges. However, there is a dearth of comprehensive prevalence statistics and knowledge on independent predictors of postmenopausal osteoporosis in India. It is estimated that approximately one in three women and one in eight men in India are affected by this condition.[1]

Osteoporosis typically arises from an imbalance between bone resorption and bone formation, often associated with postmenopausal estrogen deficiency and age-related bone loss. Other risk factors for osteoporosis include high plasma levels of parathyroid hormone (PTH), advancing age, genetic factors, cigarette smoking, alcohol consumption, physical inactivity, and prolonged use of certain medications such as corticosteroids. Low physical activity, as seen in sedentary lifestyles of elderly, paralyzed, or immobilized individuals, is also linked to accelerated bone loss. Additionally, medical conditions such as hyperparathyroidism and diabetes mellitus (DM) have been identified as risk factors for osteoporosis.[2]

At the molecular level, osteoporosis is initiated by uncoupling bone resorption and bone formation. This is mediated by various cytokines and mediators that regulate osteoclast differentiation and function, including Receptor activator of nuclear factor kappa-B ligand (RANKL), cyclooxygenase (Cox)-2, prostaglandin (PG) E2, tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, and IL-11. These factors promote preosteoblasts recruitment and differentiation, leading to enhanced bone resorption and bone loss. Therefore, increased levels of these osteoclastogenic cytokines are associated with faster progression of bone loss in osteoporosis. Identifying and addressing these risk factors is important to

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effectively manage and prevent osteoporosis. Understanding the molecular mechanisms involved in the development of osteoporosis can provide valuable insights for the development of targeted interventions to prevent and treat this condition.[2]

The objective of this review is to provide a comprehensive analysis of osteoporosis as a complex disease that frequently presents comorbidities, such as diabetes, chronic kidney disease, and menopause. Our goal is to explore the intricate interrelationships between these conditions and osteoporosis, and to highlight the necessity for a multidisciplinary approach to managing osteoporosis in these patients, in order to minimize the long-term impact on bone health and overall health outcomes.

METHODOLOGY

For this study, we conducted a systematic literature search for human studies in two electronic databases (PubMed, Cochrane). The search strategy included combinations of key terms related to type 2 diabetes mellitus (T2DM) hyperglycemia, and anti-diabetic agents (searched separately), as well as terms related to osteoporosis, fracture, bone mineral density, and anti-osteoporotic agents (also searched separately). Additionally, we included terms related to pregnancy, placenta, menopause, bone, osteoporosis, growth hormone (GH), insulin-like growth factor-1 (IGF-1), parathyroid hormone-related peptide (PTHrp), bone markers, RANKL, chronic kidney disease (CKD) and osteoprotegerin (OPG).

We also conducted a manual search of key journals and abstracts from major annual meetings in the fields of diabetes, osteoporosis, endocrinology, menopause, pregnancy, and orthopedics. Our inclusion criteria focused on studies that addressed the management of patients with T2DM and osteoporosis, as well as those specifically addressing the management of osteoporosis in the context of menopause, pregnancy, chronic kidney disease and orthopedics.

After screening the identified articles, we added 12 final articles to our review. This comprehensive analysis of the literature provides a valuable contribution to the scientific community in understanding the relationship between T2DM, menopause, and osteoporosis from multiple perspectives.

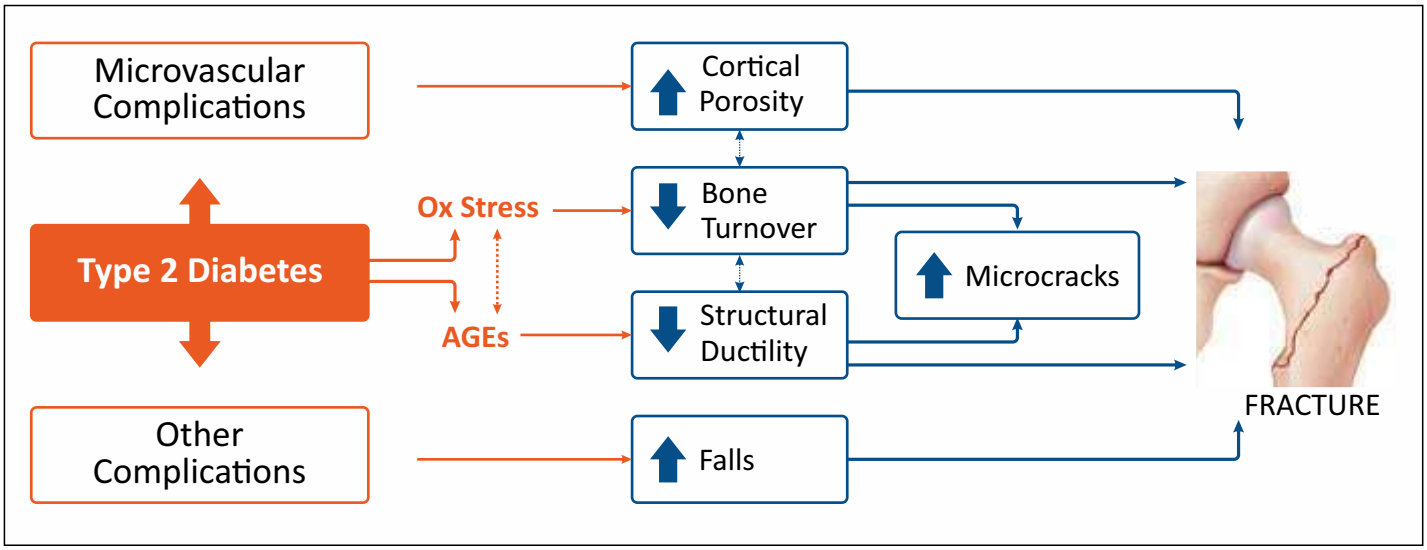
DIABETES MELLITUS AND OSTEOPOROSIS

Diabetes mellitus (DM) is a group of metabolic diseases characterized by chronic hyperglycemia due to defective insulin secretion and/or insulin action. DM is associated with dysfunction and failure of various organs, including the eyes, kidneys, nerves, heart, and blood vessels. Additionally, DM has been linked to metabolic bone diseases, such as osteoporosis and low-impact fractures, as well as falls in older adults. However, bone deterioration differs between type 1 DM (insulin-dependent DM) and type 2 DM (non-insulin-dependent DM), possibly due to different cellular and molecular mechanisms. Type 1 DM is associated with low bone mass and increased fracture risk, while data on skeletal abnormalities in type 2 DM are conflicting. Visual impairment, gait imbalance, and being overweight may contribute to fractures and falls in type 2 DM. Peripheral neuropathy in type 2 DM can also lead to Charcot osteoarthropathy, causing pain, fractures, and joint deformity. Figure 1 illustrates the underlying pathophysiological mechanisms of bone fragility in type 2 diabetes mellitus (T2DM), whereby dysregulation of glucose homeostasis leads to the accumulation of advanced glycation end-products (AGEs) in bone, resulting in increased oxidative stress. These pathological changes have a direct impact on bone health by reducing bone turnover and impairing the structural integrity of bone. Furthermore, microvascular disease and other T2DM associated complications, such as neuropathy, retinopathy, and nephropathy, contribute to bone fragility through mechanisms such as increased cortical bone porosity and an elevated risk of falls.[2,3]

MECHANISM OF DIABETES MELLITUS-INDUCED OSTEOPOROSIS

Hyperglycemia is widely recognized as a key factor that has direct and indirect detrimental effects on osteoblast function and bone formation (Figure 2). DM and hyperglycemia stimulates the production of macrophage colony-stimulating factor (MCSF), and which are osteoblast-derived activators of osteoclast proliferation and differentiation. This leads to increased osteoclast function and bone resorption.

Figure 1 - Pathophysiological Mechanisms of Bone Fragility in Type 2 Diabetes Mellitus.[3]



Additionally, DM and hyperglycemia suppress osteoblast proliferation and function by decreasing the expression of runt-related transcription factor (Runx)-2, osteocalcin, and osteopontin. Furthermore, DM and hyperglycemia promote adipogenic differentiation of mesenchymal stem cells, as evidenced by the overexpression of adipocyte differentiation markers such as peroxisome proliferator-activated receptor (PPAR)-γ, adipocyte fatty acid binding protein (aP2), adipsin, and resistin. This shift towards adipogenic differentiation at the expense of osteogenic differentiation further impairs bone health. In addition to these cellular changes, DM and hyperglycemia also contribute to reduced neovascularization, which can worsen bone loss. Moreover, the production of in DM can negatively impact bone quality, eventually leading to low-impact or fragility fractures. Overall, the complex interplay of hyperglycemia-induced changes in osteoblast and osteoclast function, adipogenic differentiation, neovascularization, and AGE production collectively contribute to the increased risk of osteopenia, osteoporosis, and fragility fractures in DM patients.[2,3]

ANTIDIABETIC DRUGS AND BONE TISSUE METABOLISM

Several drugs used in the treatment of diabetes have been shown to have an impact on bone mineral metabolism, as demonstrated in Figure 3. Metformin, a commonly prescribed medication for diabetes, has been associated with a reduced risk of fractures. In contrast, sulfonylureas, another class of antidiabetic drugs, have been linked to an increased risk of hip fractures in patients with T2DM. Insulin and Thiazolidinediones are associated with increased fracture risk. GLP-1 agonists show a reduced fracture risk, but DPP-4 inhibitors do not affect fracture risk.[4]

Figure 2 - Possible deleterious effects of diabetes mellitus on bone metabolism and bone quality.

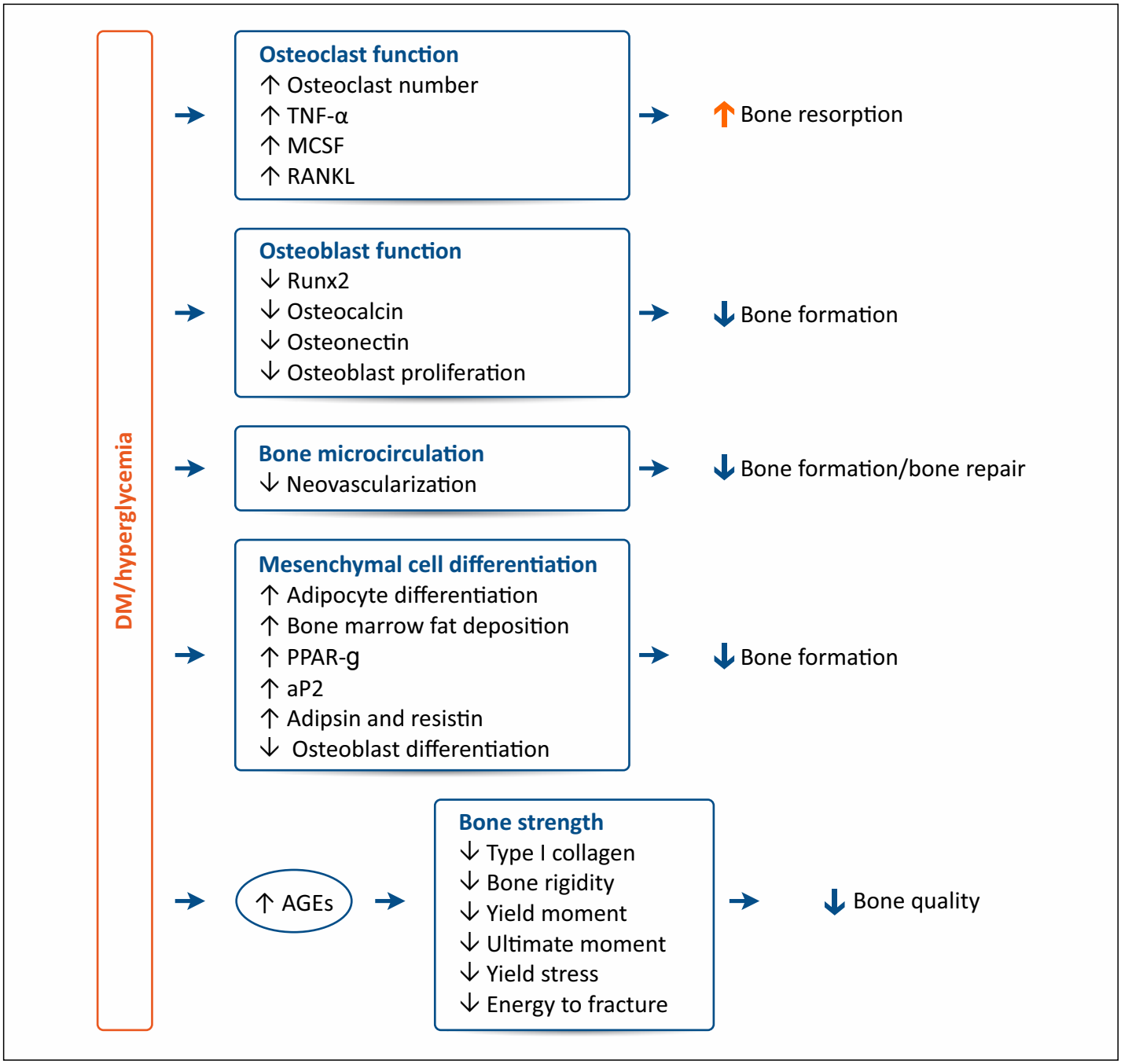
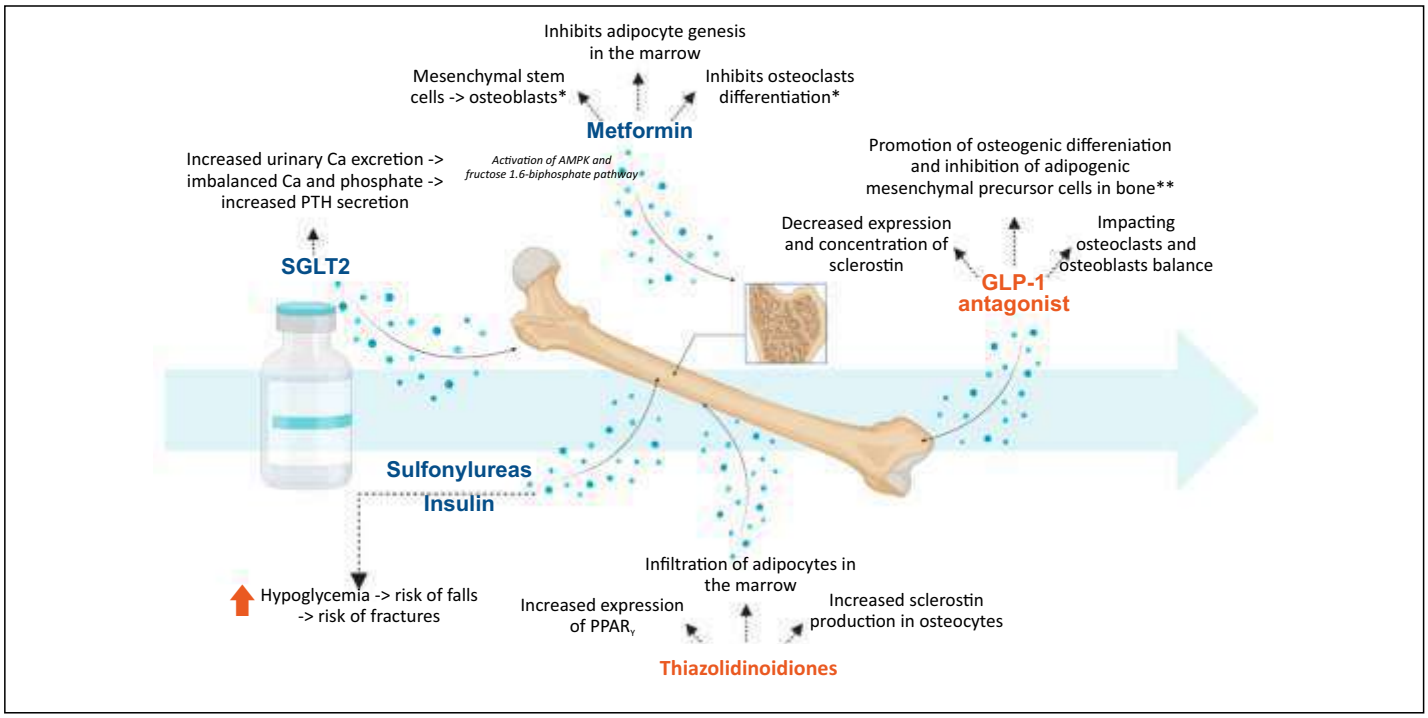


Figure 3 - Mechanism of action of drugs used in diabetes on bone mineral metabolism[4]



ANTIOSTEOPOROSIS MEDICATIONS AND GLUCOSE METABOLISM

Animal studies have shown that there is crosstalk between bone and energy metabolism, and concerns have been raised about the potential effects of antiosteoporosis drugs on glucose metabolism. However, post hoc analyses of randomized trials and observational studies have not found an increased risk of diabetes with the use of antiresorptive therapies such as alendronate, zoledronic acid, denosumab, or raloxifene. Mouse studies have suggested that blocking receptor activators of nuclear factor kappa-B ligand (RANKL) may have a favorable effect on diabetes prevention, but clinical trials did not show any correlation between denosumab treatment and glucose metabolism. PTH 1–34 has been shown to improve insulin resistance and increase serum osteocalcin in animal models, but the effects of teriparatide on glucose metabolism are inconclusive with some studies showing no effect and others showing an increase in fasting glucose and insulin resistance in postmenopausal women after 6 months of treatment.[5]

MANAGEMENT OF T2DM AND OSTEOPOROSIS

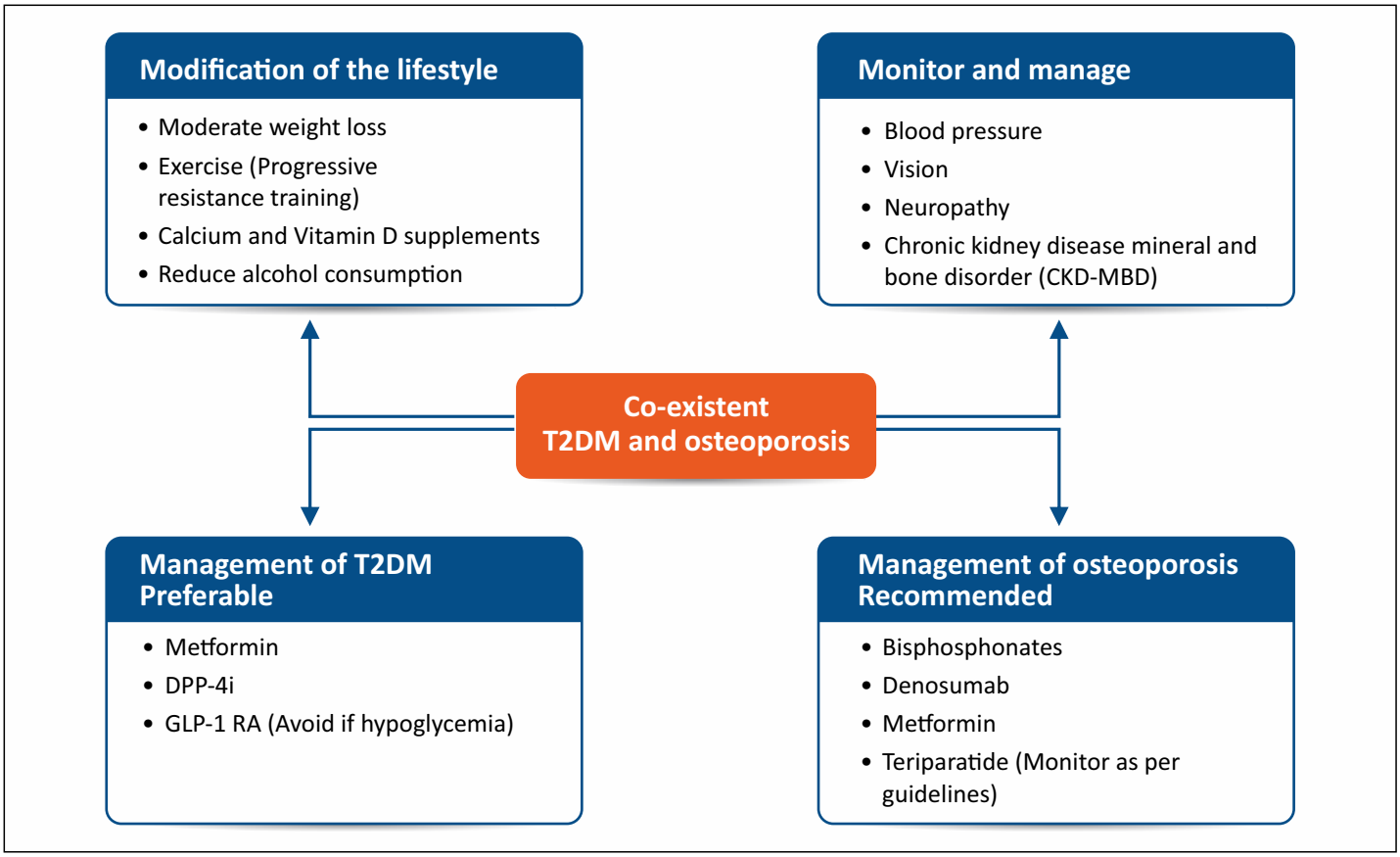
Lifestyle intervention, including medical nutrition therapy and exercise, plays a crucial role in managing type 2 diabetes mellitus (T2DM) and coexistent osteoporosis. An ideal medical nutrition therapy for both conditions includes modest weight loss, a Mediterranean-style diet rich in monounsatu rated fats, long-chain omega-3 fatty acids, nuts, and seeds, appropriate intake of calcium and vitamin D with careful consumption of fatty milk products, and limited intake of alcohol and sodium. For exercise, intense walking for at least 150 minutes per week can combine the recommended moderate-intensity aerobic exercise for T2DM with weight-bearing exercise for osteoporosis.

Pharmacologic therapy with metformin as first-line treatment is often initiated concurrently with lifestyle intervention. If HbA1c levels remain above target, a second agent should be added, with sulfonylureas, DPP-4i, or GLP-1RA preferred as second-line options in patients with T2DM and osteoporosis, while insulin should be used with caution. TZDs and canagliflozin should be avoided, and other SGLT-2i are less well-validated options. The addition of a third agent should be decided in the same context. The effect of antiosteoporotic medications on the incidence of T2DM and glucose metabolism is inconclusive, and further research is warranted. In general, the treatment and monitoring of osteoporosis should follow international guidelines, with bisphosphonates as first-line therapy, and other options like SERMs, teriparatide (PTH), and denosumab considered based on individual patient characteristics and contraindications. Figure 4 provides an outline of the management approach, summarizing the key strategies for addressing the management in a scientifically informed manner.[5]

OSTEOPOROSIS AND MENOPAUSE RELATION BETWEEN OSTEOPOROSIS AND MENOPAUSE

Loss of bone mass is a significant consequence of menopause, which can lead to the development of osteoporosis. Calcium absorption decreases with age. High salt in the Indian diet is likely to increase urinary calcium excretion. Increased absorption of calcium is probably secondary to estrogen-induced enhancement of the ability of 1,25 (OH)2D. Additionally, the lack of estrogen after menopause is directly related to the development of osteoporosis. Bone resorption outpaces the building of new bone, particularly in the first five years after menopause, which can result in up to a 10% reduction in bone mass. Early menopause, prolonged periods of low hormone levels and infrequent menstrual cycles can also increase the risk of osteoporosis.[6]

Figure 4 - Strategies for treating type 2 diabetes mellitus and concurrent osteoporosis

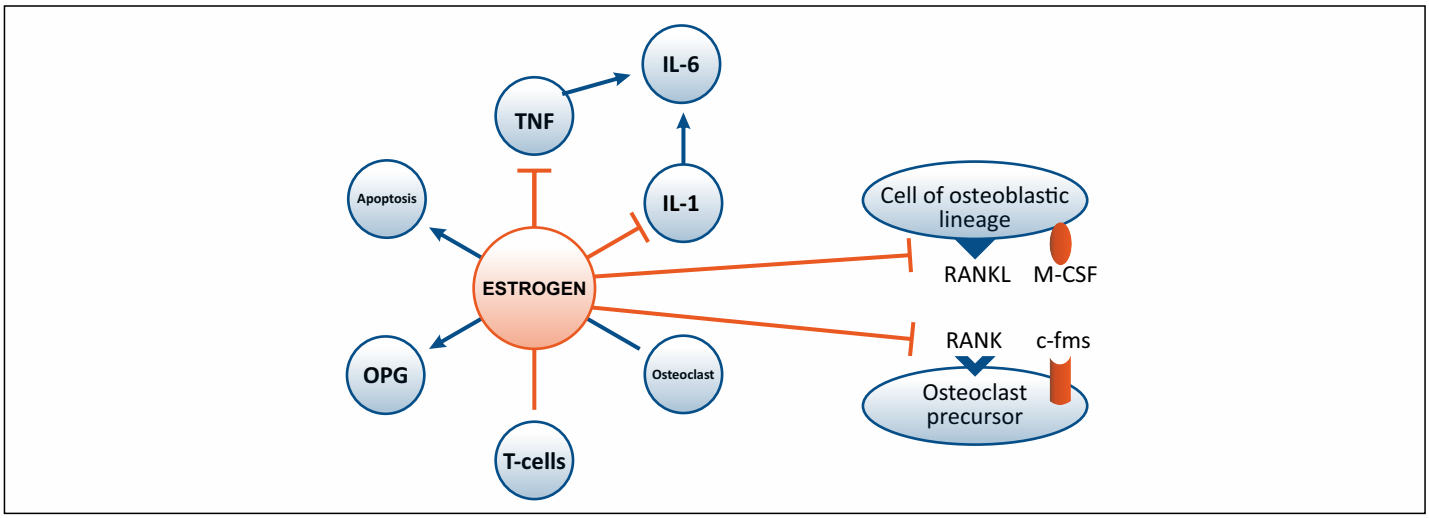


THE ROLE OF ESTROGEN IN BONE REMODELING: MECHANISMS AND EFFECTS

Postmenopausal osteoporosis is primarily caused by estrogen deficiency. Initially, it was thought that this deficiency impaired bone formation, but later studies demonstrated that it led to rapid bone resorption instead. Estrogen deficiency accelerates both processes, but resorption surpasses bone formation, resulting in a decrease in bone mass. Estrogen exhibits its bone-sparing effect through several mechanisms. It suppresses the production of IL-1 and TNF, which are potent stimulators of bone resorption and suppressors of bone formation. Additionally, estrogen inhibits the expression of IL-6, which stimulates osteoclast precursor cells and promotes osteoclastogenesis. Estrogen directly promotes the apoptosis of mature osteoclasts through the Fas/Fas ligand system and upregulation of the Fas gene. Estrogen also activates osteoprotegerin, which neutralizes factors responsible for osteoclast development and inhibits their maturation.

Furthermore, estrogen inhibits both (RANKL) and its receptor RANK, which are primary modulators of bone turnover and play a crucial role in bone loss. RANKL is primarily derived from cells of the osteoblastic lineage, and its expression is stimulated by IL-1 and TNF. Estrogen inhibits their activity, indirectly inhibiting RANKL activity. Overall, estrogen has a protective effect on bone by inhibiting the process of osteoclastogenesis and promoting osteoclast apoptosis while also activating factors that inhibit osteoclast maturation. Figure 5 illustrates the role of estrogen in bone remodeling.[7]

Figure 5 - Role of estrogen in the bone remodeling cycle



TNF, Tumor necrosis factor; IL, Interleukins; OPG, orthopantomagram RANKL, receptor activator of nuclear factor kappa-B ligand; RANK, receptor of rankl; M-CSF, Macrophage colony-stimulating factor; c-fms, Colony-stimulating factor-1 receptor

MANAGEMENT OF OSTEOPOROSIS AND MENOPAUSE

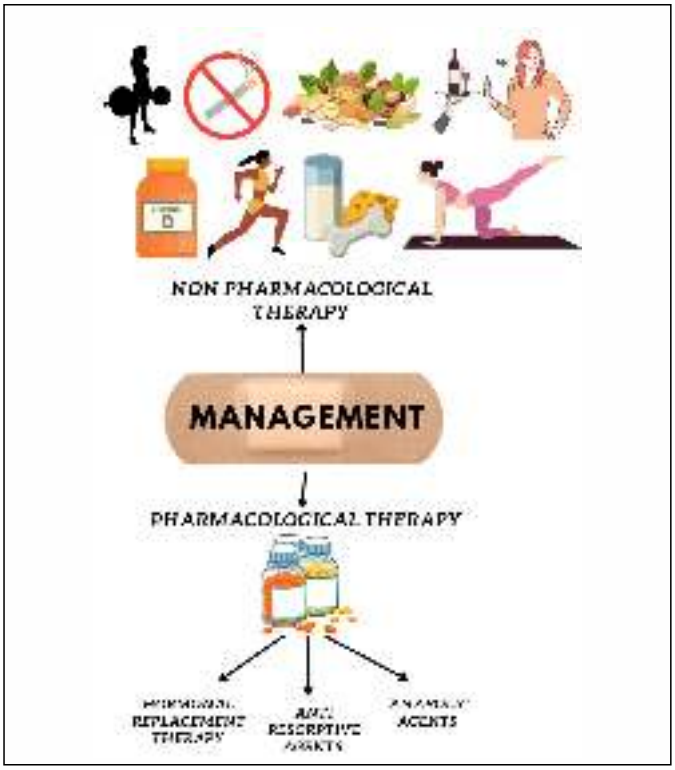
General Management

Postmenopausal osteoporosis can be managed through lifestyle modifications like a balanced diet rich in calcium and proteins, regular exercise including weight-bearing and resistance training, and avoiding smoking and alcohol consumption. Calcium and vitamin D supplements are recommended as first-line treatments, with calcium citrate maleate advised for those with reduced gastric acid secretion. Vitamin D supplementation is recommended for all postmenopausal women. Adequate protein intake and exercise can help prevent bone and muscle loss.

Pharmacological management

Pharmacological therapy for osteoporosis can be classified into three main categories: hormone replacement therapy with estrogen, anti-resorptive agents, and anabolic agents. Estrogen has both anti-resorptive and anabolic effects on bone, but its long-term use has been associated with increased risks of cardiovascular disease, venous thromboem bolism, stroke, and breast cancer. However, it can be beneficial for women with estrogen deficiency due to early menopause or primary ovarian insufficiency, as well as for those experiencing vasomotor and genitourinary symptoms. Anti-resorptive agents, such as bisphosphonates and denosumab, reduces the risk of fractures by decreasing bone loss, while selective estrogen receptor modulators (SERMs) mimic the effects of estrogen without the harmful effects on the endometrium and breast. Anabolic agents, such as teriparatide, increases the formation of new bone and can be helpful in osteoporosis. It is important to choose the appropriate therapy based on a patient's individual needs and risk factors, taking into consideration the potential risks and benefits. (Figure 6) [6-7]

Figure 6 - Management modalities of postmenopausal osteoporosis



CHRONIC KIDNEY DISEASE AND OSTEOPOROSIS

Chronic kidney disease mineral and bone disorder (CKD-MBD) is a systemic disorder of mineral and bone metabolism in patients with CKD. It involves abnormalities in vitamin D, calcium, phosphorus, or parathyroid hormone (PTH) metabolism, bone strength, linear growth, turnover, mineralization, or volume, as well as vascular or soft tissue calcifications. Renal osteodystrophy (ROD), the bone abnormalities component of CKD-MBD, increases the risk of fractures in patients with CKD. CKD-MBD is a complex disorder that includes osteoporosis but also involves other abnormalities. Patients with CKD and osteoporosis exhibit different underlying mechanisms, as shown in Figure 7. Management of osteoporosis in patients with chronic kidney disease is represented in Figure 8 [8-9]

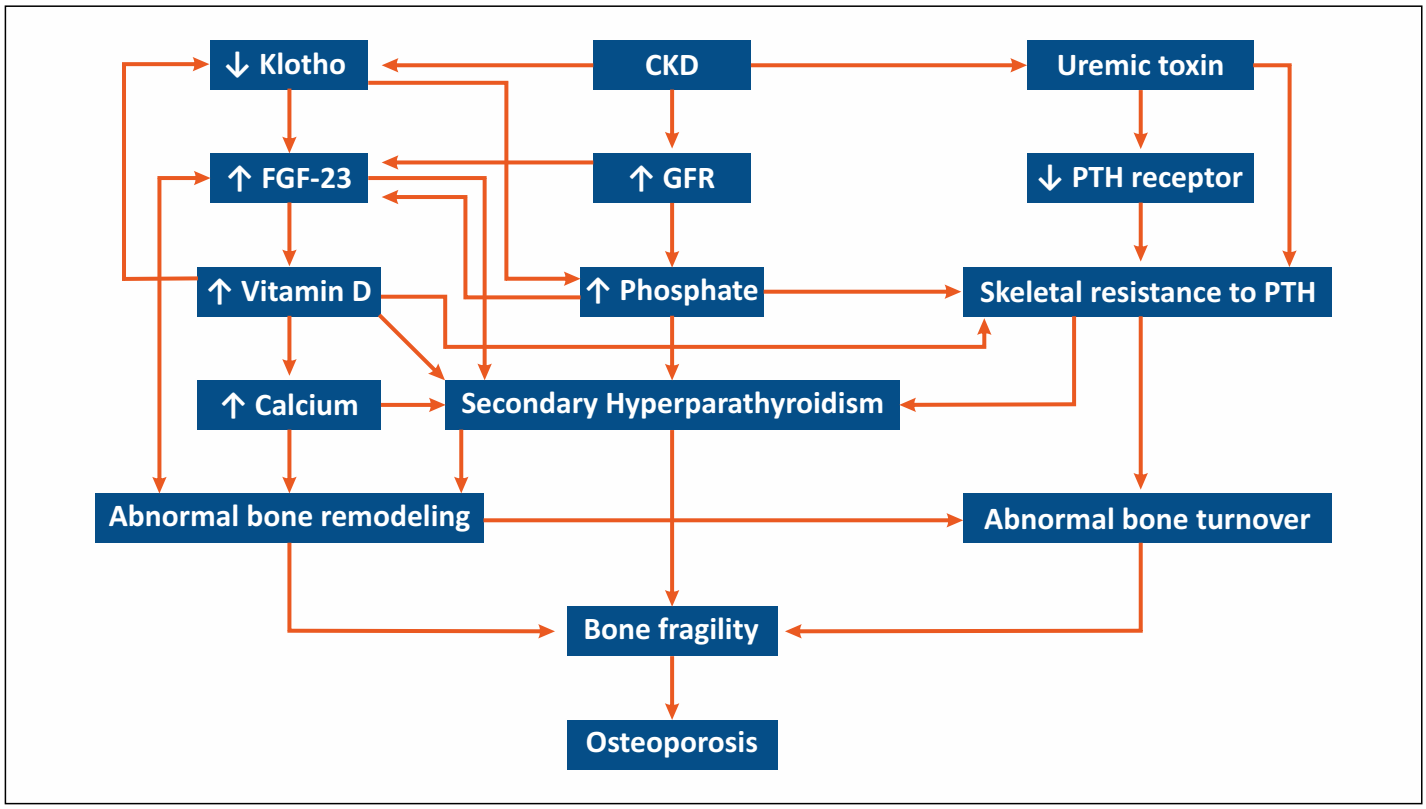
DISCUSSION

Osteoporosis is a complex disease that often coexists with other medical conditions, presenting several challenges to its management, including potential drug interactions, adverse effects, and the need for individualized treatment plans. The importance of a multidisciplinary approach to the managem ent of osteoporosis in patients with comorbidities has been highlighted in various studies. Orthopedic surgeons can play a vital role in facilitating osteoporosis treatment by coordinating care with primary care providers and families of patients with fragility fractures. Proper management of the current fracture, evaluation of reversible risk factors for osteoporosis, and the development of an appropriate follow-up plan are all critical steps that orthopedic surgeons can take to ensure that patients receive appropriate osteoporotic treatment and reduce the risk of subsequent fractures. Early detection and screening for osteoporosis in patients with coexisting medical conditions are crucial to prevent further complications.

Furthermore, nutrition plays a crucial role in patients with fragility fractures. Malnutrition is prevalent in patients with acute hip fractures, particularly those admitted to an orthogeriatric program. Frailty and pre-frailty have been shown to be significantly associated with a higher risk of future falls, especially with increasing age. Therefore, routine nutritional assessments should be conducted to combat this issue. Although isolated nutritional interventions have not consistently shown significant impact on long-term outcomes after hip fracture, multidisciplinary nutritional care has been demonstrated to reduce nutritional deterioration over admission and increase the rate of discharge back to the community setting.

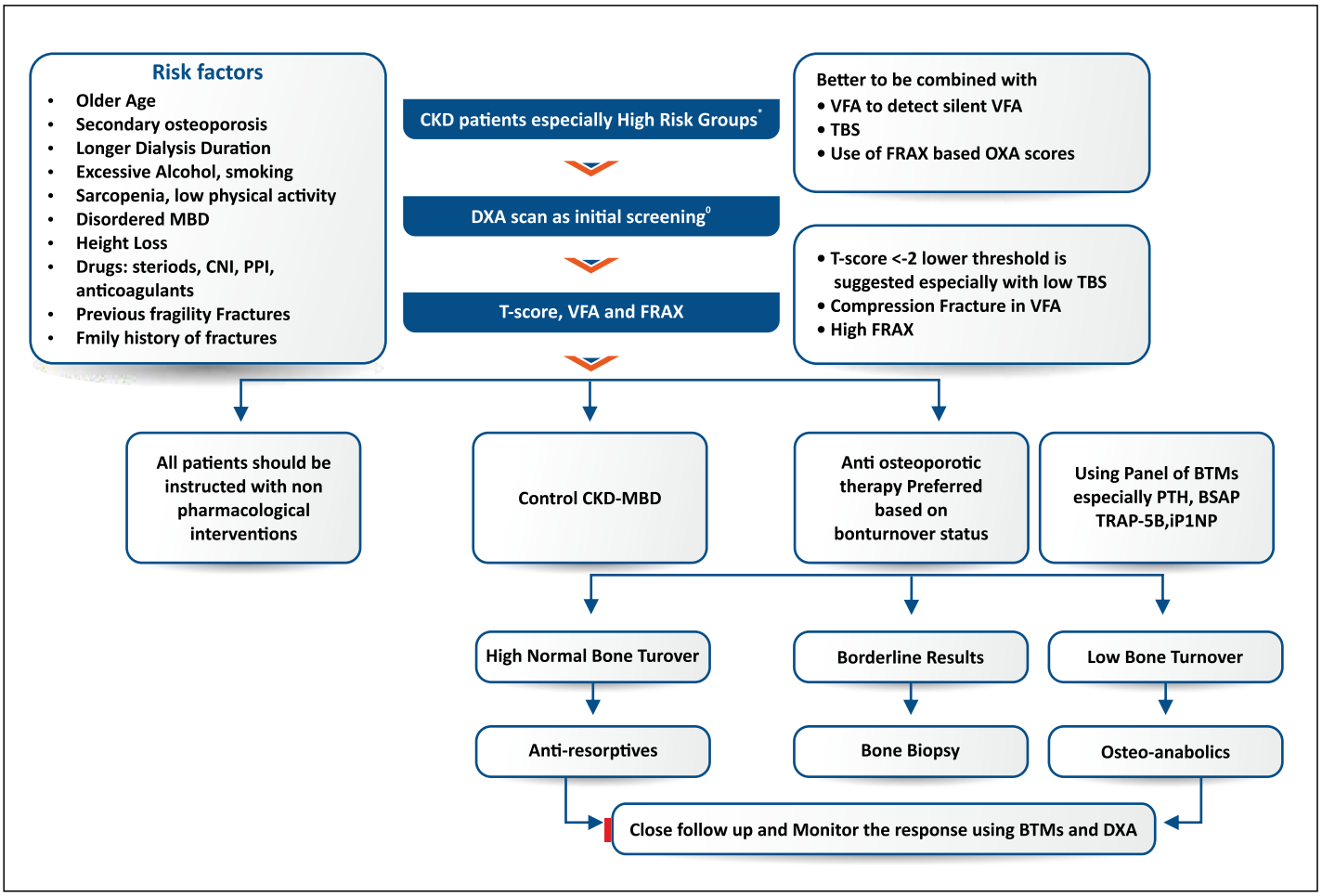
The management of osteoporosis in patients with coexisting medical conditions requires individualized treatment plans tailored to the specific needs of each patient. For instance, patients with chronic kidney disease may require alternative treatment options due to the potential for medication toxicity and impaired drug clearance. Similarly, in patients with type 2 diabetes, medication selection must take into account the risk of hypoglycemia, which may be exacerbated by certain osteoporosis medications. Early

Figure 7 - **Different mechanisms in CKD lead to osteoporosis**



FGF-23: fibroblast growth factor, GFR: glomerular filtration rate, PTH: parathyroid hormone[8]

Figure 8 - Management of osteoporosis in patients with chronic kidney disease[9]



MBD, mineral and bone disorder; CNI, calcineurin inhibitors; PPI, proton pump inhibitor; VFA, Vertebral fracture assessment; TBS, Trabecular bone score; FRAX, Fracture Risk Assessment Tool; BTM, Bone turnover markers; PTH, parathyroid hormone; BSAP, bone-specific alkaline phosphatase; TRAP-5B, Tartrate-resistant acid phosphatase 5b; iP1NP, procollagen type 1 N propeptide; DXA, dual-energy x-ray absorptiometry

detection and screening for osteoporosis in patients with comorbidities are crucial for optimal management, as is ongoing monitoring and assessment of bone health. Despite the challenges, addressing these issues through a collaborative approach can lead to improved outcomes and reduced risk of subsequent fractures in this population.

In conclusion, managing osteoporosis in patients with coexisting medical conditions requires a multidisciplinary approach, involving orthopedic surgeons, primary care providers, nutritionists, and other healthcare professionals. Early detection and screening, ongoing monitoring, and individualized treatment plans are critical to optimize management and prevent further complications. Adhering to this approach will lead to improved outcomes and reduced risk of subsequent fractures in this population.[10-12]

CONCLUSION

Osteoporosis is a multi-faceted disease that often coexists with other medical conditions, such as diabetes, chronic kidney disease, and menopause. The complex interplay between these conditions highlights the need for a multidisciplinary approach to the management of osteoporosis. The involvement of a team of healthcare professionals, including endocrinologists, nephrologists, gynecologists, primary care physicians, and physical therapists, can help to reduce the long-term impact of osteoporosis on bone health and overall health outcomes. A collaborative approach that addresses the unique needs of each patient can lead to better outcomes and improve the quality of life for individuals living with osteoporosis and other medical conditions. Therefore, a team or multidisciplinary management approach is necessary for the effective management of osteoporosis and its associated conditions.

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