Int. J. Pharm. Investigation, 2026; 16(3):843-858.
https://www.jpionline.org

Review Article

Medications and Bone Health: A Comprehensive Review of Skeletal Risks and Therapeutic Approaches

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ABSTRACT

Bone-drug interactions represent a critical yet often under recognized domain within clinical pharmacology due to their long-term implications on skeletal integrity. The human skeletal system relies on a tightly regulated balance between bone formation and resorption. Disruption of this balance by commonly prescribed medications can result in reduced Bone Mineral Density (BMD), compromised bone structure, and an elevated risk of fractures. This review aims to evaluate the mechanisms, clinical consequences, and therapeutic strategies related to drug-induced bone disorders, focusing on widely used medications such as glucocorticoids, Antiepileptic Drugs (AEDs), Proton Pump Inhibitors (PPIs), chemotherapeutic agents, and hormonal therapies. Glucocorticoids suppress osteoblast function and enhance osteoclast activity, causing net bone loss. AEDs impair vitamin D and calcium metabolism via cytochrome P450 enzyme induction. PPIs reduce calcium absorption by altering gastric pH, affecting bone mineralization. Chemotherapeutic agents disrupt both osteoblast and osteoclast function, accelerating bone turnover. Hormonal therapies such as aromatase inhibitors and androgen deprivation therapy exacerbate bone loss, especially in oncology patients. High-risk groups include postmenopausal women, elderly individuals, and patients on chronic drug therapy. Conclusion: Bone-drug interactions significantly contribute to conditions like osteopenia, osteoporosis, and fragility fractures. Clinical management involves early detection using BMD tests and biochemical markers, lifestyle interventions (exercise, smoking cessation), and nutritional support (calcium and vitamin D). Pharmacological agents such as bisphosphonates, SERMs, and denosumab are effective in preventing drug-induced bone loss. Personalized medicine approaches especially those incorporating genetic risk profiling can optimize treatment decisions and minimize adverse skeletal outcomes. Multidisciplinary collaboration and further research into safer drug formulations and targeted therapies are vital to safeguard bone health in vulnerable populations.

Keywords: Bone-drug Interactions, Osteoporosis, Glucocorticoids, Bone Metabolism, Fracture Risk, Pharmacological Management.

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Received: 16-01-2026;
Revised: 09-04-2026;
Accepted: 21-05-2026.

INTRODUCTION

Bone health is essential for maintaining structural integrity, mobility, and overall quality of life. In addition to supporting and shielding important organs, bones also store minerals like calcium and phosphorus, which are essential for many physiological functions. Healthy bones are critical for preventing conditions such as osteoporosis and fractures, which can lead to chronic pain, reduced mobility, and increased mortality, especially in older populations. Maintaining bone health through proper nutrition, physical activity, and early interventions is vital for long-term skeletal strength and overall well-being (Mehta *et al.*, 2023). Bone strength and health are largely dependent on an ongoing process of bone turnover. Bone strength declines and fractures occur if bone resorption outpaces bone production (Bharadwaj *et al.*, 2024). Millions of people worldwide are impacted by bone illnesses like osteoporosis, osteosarcoma (Prithiksha *et al.*, 2024), and fractures, which are especially common in the elderly and postmenopausal women. Osteoporosis alone is responsible for over 8.9 million fractures annually, leading to disability, chronic pain, and loss of independence. Hip fractures, a common outcome, are associated with high mortality rates within the first year. The economic impact is substantial, with healthcare systems incurring billions in costs for treatment, rehabilitation, and long-term care. Beyond the financial strain, bone diseases significantly reduce the quality of life, highlighting the urgent need for prevention, early detection, and effective management strategies (Senthil,

DOI: 10.5530/ijpi.20260055

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2024). Drug-induced effects on bone metabolism have become a growing concern in medical practice due to the widespread use of medications that inadvertently compromise bone health. The equilibrium between bone formation and resorption can be upset by commonly prescribed medications such glucocorticoids (Yadalam *et al.,* 2024), antiepileptics (Bose *et al.,* 2024), proton pump inhibitors (Philippoteaux *et al.,* 2024), and chemotherapy. These consequences raise the risk of fracture, cause secondary osteoporosis, and reduce bone mineral density (Jeyashree *et al.,* 2023). With the aging population and rising prevalence of chronic conditions requiring long-term medication, drug-induced bone loss poses a significant public health challenge. Addressing this issue requires increased awareness, proactive monitoring, and integration of preventive strategies into clinical care. This review explores the mechanisms, implications, and management strategies for bone-drug interactions.

METHODOLOGY

This review was conducted through a comprehensive literature survey focusing on drug-induced bone disorders and bone-drug interactions. Relevant scientific articles were sourced from established databases including PubMed, Scopus, ScienceDirect, and Web of Science. The search strategy involved the use of keywords and Medical Subject Headings (MeSH) terms such as "bone-drug interaction," "osteoporosis," "bone mineral density," "glucocorticoids," "antiepileptic drugs," "proton pump inhibitors," "chemotherapeutic agents," "hormonal therapy," "fracture risk," and "bone loss." Articles published were included to ensure the incorporation of recent findings. Studies were selected based on their relevance to drug mechanisms affecting bone remodeling, clinical manifestations of bone disorders associated with pharmacological agents, and available strategies for management or prevention. Reviews, meta-analyses, clinical trials, *in vivo* studies, and *in vitro* experiments were all considered to provide a holistic view of the subject. Data were extracted, categorized, and analyzed under specific themes including drug classes, underlying pathophysiological mechanisms, clinical consequences, high-risk populations, and current therapeutic interventions. The gathered information was critically evaluated to synthesize current knowledge and identify gaps in research. Emphasis was placed on multidisciplinary approaches, precision medicine, and emerging strategies aimed at minimizing skeletal complications related to long-term pharmacotherapy.

MECHANISMS OF BONE-DRUG INTERACTIONS

Drugs Affecting Bone Formation

Glucocorticoids

Steroid hormones called Glucocorticoids (GCs) react to stress and the circadian rhythm. When the Hypothalamic-Pituitary-Adrenal (HPA) axis is activated, the adrenal glands release endogenous GCs. Low bone mass and an elevated risk of fracture are caused by either Cushing's syndrome, Addison's disease, or excessive or insufficient levels of endogenous GCs (Batista *et al.,* 2019; Kaltsas *et al.,* 2010; Løvås *et al.,* 2009; Björnsdottir *et al.,* 2011; Devogelaer *et al.,* 1987). Glucocorticoids (GCs) negatively impact bone homeostasis by suppressing osteoblast activity and enhancing osteoclast activity, increasing the risk of osteoporosis and causing bone loss. By inhibiting the Wnt/β-catenin signalling pathway, they prevent osteoblast differentiation and encourage Mesenchymal Stem Cells (MSCs) to differentiate into adipocytes rather than osteoblasts (Figure 1). GC signalling in osteoblast-lineage cells is essential for maintaining bone mass, as demonstrated by a number of animal models. By overexpressing 11b-HSD2, the enzyme that causes GC inactivation, the impact of inactivated GC signalling in mature osteoblasts and osteocytes was examined. Mice's cortical and trabecular bone mass was decreased by a 2.3 kb or 3.6 kb segment of the Col1a1 promoter-driven overexpression of 11bHSD2 (Col2.3-HSD2 or Col3.6-HSD2), indicating the significance of GC signalling in osteoblast-lineage cells to control bone mass (Kalak *et al.,* 2009; Yang *et al.,* 2010). The most frequent cause of secondary osteoporosis, which raises the risk of fractures, is long-term GC medication (Staa *et al.,* 2000; Weinstein, 2012). It has been demonstrated that exogenous GCs administered to patients at doses more than 2.5 mg for longer than three months impair bone quality (Messina *et al.,* 2022). Additionally, it is well established that exogenous GCs prevent osteogenesis (Ahmad *et al.,* 2019; Chotiyarnwong *et al.,* 2020). Impaired osteogenesis was seen in Bone Marrow Stromal Cells (BMSCs) obtained from patients with corticosteroid-induced osteonecrosis (Houdek *et al.,* 2016). BMSCs extracted from a rat GIO model also showed reduced osteogenic differentiation and proliferation (Zhou *et al.,* 2014). Low bone mass resulted from the application of exogenous GCs *in vivo*, which inhibited osteoblast development and proliferation and caused osteoblast and osteocyte apoptosis (O'Brien *et al.,* 2004; Rauch *et al.,* 2010). Patients on long-term GC treatment are known to have a markedly elevated risk of bone fractures (Staa *et al.,* 2000; Kobza *et al.,* 2021). Preclinical research suggests that GCs also affect the intricate fracture healing process, despite the fact that steroid usage has not been identified in clinical investigations as a significant risk factor for non-union fracture healing (Zura *et al.,* 2016). This holds true for both GC treatment and endogenous GCs, which regulate several physiological functions and are secreted as stress hormones in response to bone fractures. All phases of bone fracture healing are expected to be impacted by endogenous and exogenous or excessive GCs, which calls for a precisely calibrated interaction between several cell types, including immune, bone, and stromal cells all of which are critically regulated by GCs (Ahmad *et al.,* 2019; Hachemi *et al.,* 2018). By decreasing intestinal calcium absorption and raising renal calcium excretion, Glucocorticoids (GCs) disrupt calcium homeostasis. They downregulate calcium transport proteins and suppress calcitriol production, leading to

decreased calcium uptake. Simultaneously, GCs enhance renal calcium loss by inhibiting reabsorption in the kidneys, causing hypocalcemia. This trigger increased Parathyroid Hormone (PTH) secretion, promoting bone resorption and increasing osteoporosis risk (Downie *et al.,* 2022). Therapeutic strategies to mitigate these effects include bisphosphonates, which inhibit osteoclast-mediated bone resorption, denosumab, which blocks RANKL to prevent osteoclast activation, and teriparatide, a recombinant Parathyroid Hormone (PTH) that stimulates osteoblast activity. Supplementing with calcium and vitamin D is also essential for preserving bone health, as are lifestyle changes like quitting smoking and engaging in weight-bearing activities.

Antiepileptic Drugs (AEDs)

Antiepileptic Drugs (AEDs) can disrupt vitamin D metabolism by inducing Cytochrome P450 (CYP) enzymes, particularly CYP3A4, CYP2C9, and CYP2C19, which accelerate the breakdown of vitamin D. Reduced serum levels of calcidiol (25-hydroxyvitamin D) and calcitriol (1,25-dihydroxyvitamin D) result from this elevated metabolism, which may cause bone demineralisation and poor calcium absorption. Due to a prolonged vitamin D insufficiency, long-term use of enzyme-inducing AEDs like phenytoin, carbamazepine, and phenobarbital is linked to an increased risk of osteomalacia, osteoporosis, and fractures (Fan *et al.,* 2016) (Figure 2). Bone pain, muscle weakness, and fractures with little to no trauma are symptoms of people with AED-associated bone disorders. It is not until the initial fracture that these symptoms manifest (Cock, 2003). Serum levels of phosphorous, Ca2+, alkaline phosphatase, and vitamin D metabolites may be aberrant, according to their biochemical tests. If the Bone Mass Density (BMD) is reduced by less than 30%, routine X-rays are unable to detect certain bone disorders, although they can reveal bone fractures (Abeş *et al.,* 2003). Unexpected drug-drug interactions may result from the induction or suppression of CYP450 caused by AEDs given parenterally or non-parenterally (Meier *et al.,* 2011). According to reports, Enzyme-Inducing AEDs (EIAEDs) may cause CYP450 to speed up the breakdown of vitamin D, which could lead to hypocalcaemia (Gough *et al.,* 1986; Pack *et al.,* 2004; Pack *et al.,* 2003), a decrease in bone mineral density, and an increased risk of fractures (Vestergaard, *et al.,* 2004; Sheth *et al.,* 2007). Furthermore, although the effects of supplements on osteopathy due to AEDs are debatable, calcium and vitamin D supplements are nevertheless advised for epileptic patients using AEDs (Miziak *et al.,* 2014). Due to a prolonged vitamin D shortage, long-term use of enzyme-inducing AEDs like phenytoin, carbamazepine, and phenobarbital is linked to an increased risk of osteomalacia, osteoporosis, and fractures. To counteract these effects, patients on long-term AED therapy are often advised to supplement with vitamin D and calcium while monitoring bone health regularly.

Chemotherapeutics

Chemotherapeutic agents significantly impact bone remodeling by inhibiting bone progenitor cells and enhancing osteoclast activity, particularly in patients with metastatic bone disease (Figure 3). Many chemotherapeutic drugs, such as methotrexate, cyclophosphamide, and doxorubicin, exert cytotoxic effects on rapidly dividing cells, Including bone marrow osteoprogenitor cells and mesenchymal stem cells. As a result, bone production is significantly decreased and osteoblast differentiation is suppressed (Dai *et al.,* 2022). However, by upregulating the production of pro-resorptive cytokines such RANKL, TNF-α, and IL-6, which are frequently released by tumour cells or as a result of the host's inflammatory response, chemotherapeutics might indirectly encourage osteoclastogenesis (Jakovljevic *et al.,* 2023). Tumour cells worsen this imbalance in cancers that frequently spread to bone, like lung, breast, and prostate cancers, by releasing substances that increase osteoclast activity and cause excessive bone resorption. Skeletal-Related Events (SREs), such as bone pain, pathological fractures, spinal cord compression, and hypercalcemia, are exacerbated by this disturbance of normal bone turnover. The cumulative effects of reduced bone formation and increased bone resorption result in weakened bone integrity and significantly affect patients' quality of life (Silva *et al.,* 2011). Bone-targeted treatments like RANKL inhibitors (like denosumab) and bisphosphonates (like zoledronic acid) are frequently used in combination with chemotherapy regimens to lessen these side effects (Sousa *et al.,* 2018). In cancer patients with bone metastases, these substances help prevent osteoclast-mediated bone resorption, maintain bone mass, and lower the risk of skeletal problems.

DRUGS ENHANCING BONE RESORPTION

Proton Pump Inhibitors (PPIs)

Reduced stomach acid output from Proton Pump Inhibitors (PPIs) can hinder calcium absorption and have a detrimental effect on bone health (Figure 4). For best solubility and absorption in the small intestine, calcium especially calcium carbonate needs an acidic environment. PPIs lower calcium ionisation by raising stomach pH, which lowers bioavailability and may result in calcium shortage (Hussain *et al.,* 2021). Lower bone mineral density and a higher risk of fractures, especially in the hip and spine, have been linked to long-term PPI usage. The reduced calcium absorption may also trigger secondary hyperparathyroidism, further contributing to bone loss. It is debatable if taking PPIs increases the risk of fractures (Thong *et al.,* 2019). According to retrospective research, PPIs may have a dose-dependent association with reduced bone mineral density, which raises the risk of fractures, particularly hip fractures. Patients who have a risk factor for osteoporosis, such as renal impairment, seem to be at a higher risk. In order to prevent osteoporotic fractures, PPI users are advised to engage in routine osteoporosis

prophylaxis (Thong *et al.,* 2019; Poly *et al.,* 2019; Vestergaard *et al.,* 2006). More recent prospective investigations, however, found no appreciable changes in fracture risk or bone mineral density in PPI users over the short to medium term (Moayyedi *et al.,* 2019; Targownik *et al.,* 2017). Hypochlorhydria-associated malabsorption of calcium (whose absorption is essential for preserving bone microstructure), gastrin-induced parathyroid hyperplasia, and inhibition of bone resorption by blocking local H+/K+ ATPase are some of the hypothesised mechanisms that connect long-term PPI-based therapy with decreased bone mineral density (Schinke *et al.,* 2009; Al Menhali *et al.,* 2017; Tuukkanen *et al.,* 1986).To minimize these risks, patients on long-term PPI therapy are often advised to consume calcium citrate, which is less dependent on stomach acid for absorption, along with adequate vitamin D supplementation and lifestyle modifications to support bone health.

Thyroid Hormones

Increased bone turnover and consequent bone loss can result from excess thyroid hormone, whether it comes from hyperthyroidism or overuse of thyroid hormone replacement medication. Although osteoblast and osteoclast activity are both stimulated by thyroid hormones, osteoclast-mediated bone resorption tends to rise more quickly than bone production, leading to a net loss of bone mass. In individuals receiving excessive doses of levothyroxine, particularly postmenopausal women, the elevated thyroid hormone levels can accelerate bone remodeling cycles, decrease bone mineral density and raise the risk of fractures and osteoporosis. In cortical bones, such those in the hip and forearm, the effect is more noticeable. Thyroid hormones are essential for the skeleton's linear development. To reach peak bone mass, they are required (Bassett *et al.,* 2003). However, too many thyroid hormones throughout childhood can cause growth plates and cranial sutures to accumulate too quickly, which can ultimately result in short stature and craniosynostosis (Bassett *et al.,* 2003; Harvey *et al.,* 2022; Bassett *et al.,* 2008; Stevens *et al.,* 2003). Adults with overt hyperthyroidism experience a 10-20% decrease in mineral density, primarily in cortical bone, and an acceleration of bone turnover (Bassett *et al.,* 2003; Harvey *et al.,* 2022; Stevens *et al.,* 2003). The ratios of bone production to bone resorption are thrown off, and the bone remodelling cycle is cut short by about 50% (from 200 to 113 days) (Kosinska *et al.,* 2005). Over 10% of mineralised bone is lost in a single cycle because to the reduction in the bone production phase in 2/3 (Hyppönen *et al*., 2001). Thyrotoxicosis thus raises the incidence of fractures (Bassett *et al.,* 2003; Harvey *et al.,* 2022; Kosińska *et al.,* 2005; Lakatos, 2003). Individuals with hyperthyroidism have elevated serum levels of IL-6 (Reddy *et al.,* 2012; Lakatos *et al.,* 1997). IL-6 may act as a modulator of parathyroid hormone on bone tissue and promotes the formation of osteoclasts (Reddy *et al.,* 2012; Lakatos *et al.,* 1997). Hyperthyroidism's detrimental effects on bone metabolism are linked to hypercalcemia, hypercalciuria, and a negative calcium balance (Harvey *et al.,* 2002; Reddy *et al.,* 2012). Growth retardation or even growth halt, endochondral ossification abnormalities, delayed bone age, and permanent low stature are all consequences of untreated childhood hypothyroidism (Bassett *et al.,* 2003; Harvey *et al.,* 2022; Stevens *et al.,* 2003). General hypometabolism is a symptom of hypothyroidism (Kosińska *et al.,* 2005). 50% of bone production processes and 40% of bone resorption processes are slowed (Kosińska *et al.,* 2005). Blood levels of parathyroid hormone and vitamin D may rise, although calciuria is lowered and blood levels of osteocalcin and alkaline phosphatase are decreased (Kosińska *et al.,* 2005). Following thyroidectomy and radioactive iodine therapy, individuals with differentiated thyroid cancer are treated with suppressive dosages of L-T4. The consequences of supraphysiological dosages of levothyroxine on bone are still being debated, despite the fact that endogenous hyperthyroidism is a risk factor for secondary osteoporosis. In contrast to men and premenopausal women, postmenopausal women who had long-term suppressive thyroxine replacement therapy showed a decline in BMD and an increased risk of osteoporosis (Heemstra *et al.,* 2006). Careful monitoring of thyroid hormone levels and adjusting the dose to maintain a euthyroid state are essential to minimize adverse skeletal effects and preserve long-term bone health.

DRUGS CAUSING STRUCTURAL DAMAGE

Heparin

Heparin, especially when used long-term or in high doses, can cause structural damage to bone by reducing bone formation and increasing osteoclast activity (Chowdhury *et al.,* 1992) (Figure 5). It interferes with osteoblast function, leading to decreased bone matrix production and impaired bone formation. At the same time, heparin promotes osteoclast differentiation and activity, enhancing bone resorption. A net loss of bone mass is the outcome of this imbalance between bone creation and breakdown, which raises the risk of osteoporosis and fractures, especially in the vertebrae, and lowers bone mineral density (Irie *et al.,* 2007). The risk is higher with unfractionated heparin compared to Low-Molecular-Weight Heparins (LMWHs). Regular monitoring of bone health and considering alternative anticoagulation strategies when appropriate are important in patients requiring prolonged heparin therapy.

SSRIs

A higher incidence of fractures and decreased bone density have been linked to Selective Serotonin Reuptake Inhibitors (SSRIs), which are frequently prescribed to treat anxiety and depression (Bliziotes, 2010). It is believed that serotonin's function in bone metabolism is connected to this impact. While serotonin in the brain supports mood regulation, peripheral (gut-derived) serotonin has been shown to negatively influence bone formation. SSRIs increase serotonin levels systemically, which may inhibit

osteoblast activity and promote bone resorption.. According to studies, long-term SSRI usage may increase the risk of fracture and reduce bone mineral density, especially in older persons (Tsapakis *et al.,* 2012). Therefore, clinicians often weigh the benefits of SSRIs against potential skeletal risks, especially in patients with existing osteoporosis or other bone-related concerns.

IMPLICATIONS OF BONE-DRUG INTERACTIONS

Clinical Manifestations

The most prominent clinically important consequence of bone-drug interactions is an elevated incidence of fractures, especially in the wrist, hip, and spine (Márquez-Grant *et al.,* 2022). Drug-induced osteoporosis or decreased bone mineral density, which weakens the skeleton, are frequently the causes of these fractures. For example, patients on long-term corticosteroid therapy have a significantly increased risk of hip and vertebral fractures because of restricted bone growth and rapid bone resorption. Similarly, drugs like proton pump inhibitors and certain antiepileptics may impair calcium absorption or vitamin D metabolism, indirectly contributing to bone fragility (Valsamis *et al.,* 2006). The consequences of these fractures can be severe, especially in older adults, leading to chronic pain, reduced mobility, impaired quality of life, and increased morbidity and mortality. Furthermore, the importance of monitoring bone health in patients receiving long-term pharmacotherapy that affects bone metabolism is further highlighted by delayed fracture healing and increased susceptibility to complications like osteonecrosis of the jaw (particularly with bisphosphonates and denosumab) (Iscan *et al.,* 2013). The development of secondary osteoporosis, in which bone loss is caused by underlying illnesses or the use of certain medications rather than ageing alone, is another condition in which it plays a major role (Komaba *et al.*, 2021). One of public health's top priorities is managing osteoporosis. About one-third of women over 50 have the condition, and the cumulative lifetime risk of hip, forearm, or vertebral fractures is about 50%, which is comparable to the risk of cardiovascular disease (Cooper *et al.,* 2012). Due to changes in the population's demographics, the total direct costs in Europe are predicted to almost quadruple by 2050, from an estimated €31.7 billion in 2000 (Melton *et al.,* 2003). It is obvious that safe and effective treatments are necessary to lessen this load. Vertebral and nonvertebral fractures are the result of osteoporosis and are linked to high rates of morbidity and disability as well as an increase in mortality in the case of hip and vertebral fractures. The goal of treatment should be to reduce fracture risk as much as possible while minimising the likelihood of side effects. People on acid-suppressant drugs (proton pump inhibitors) have been shown to have an apparent increased incidence of fracture, but not those taking histamine H2-receptor antagonists (Vries *et al.,* 2009). Compared to patients on bisphosphonates alone, this risk increase persisted in those taking acid-suppressant drugs in addition to bisphosphonates. This problem needs more research because of the nature of the risk. Several commonly prescribed drugs can disrupt normal bone remodeling processes, leading to decreased bone mineral density and structural deterioration. Glucocorticoids are among the most well-documented causes, as they inhibit osteoblast function, increase osteoclast-mediated bone resorption, and reduce calcium absorption, all contributing to rapid bone loss (Delany *et al.,* 1994). Similar to this, hepatic enzymes induced by anticonvulsants such phenytoin and phenobarbital speed up the metabolism of vitamin D, resulting in calcium shortage and poor bone mineralisation (Fitzpatrick, *et al.,* 2004). Through a variety of methods, other substances such as Selective Serotonin Reuptake Inhibitors (SSRIs), proton pump inhibitors, and several chemotherapeutic medications can also change bone homeostasis (Franco *et al.,* 2020). Without proper bone-protective measures, long-term use of these drugs might greatly raise the risk of secondary osteoporosis, especially in susceptible groups like older adults and postmenopausal women. Early identification and management of these drug-induced effects are essential to prevent long-term skeletal complications. It can significantly impair the natural process of fracture

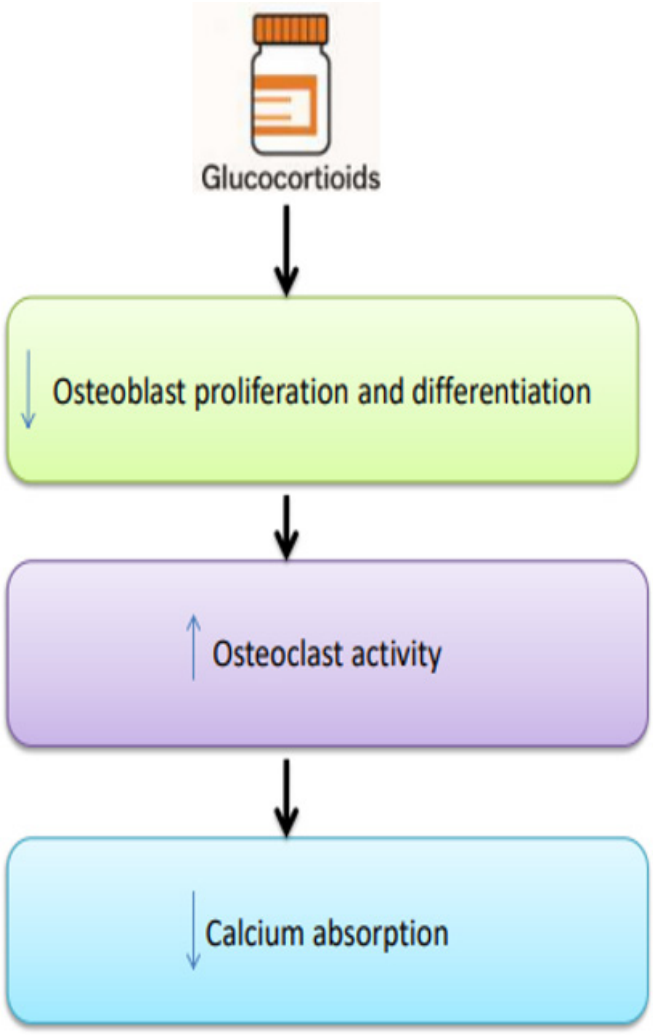

Figure 1: Effect of Glucocorticoids on Bone Formation.

healing and degrade overall bone quality. Certain medications interfere with the cellular and molecular events necessary for bone regeneration, such as inflammation, callus formation, and remodeling. Since the nineteenth century, Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), which are among the most widely used medications worldwide, have been used to treat pain by inhibiting cyclooxygenase enzymes and reducing prostaglandin synthesis. This can delay early inflammatory responses that are necessary for fracture repair (Rainsford, 2007). NSAIDs are now the safest and most efficient medications for treating postoperative pain, with very few exceptions (Bandolier *et al.,* 2003). Notwithstanding these advantages, NSAIDs are frequently avoided after orthopaedic surgeries since they are believed to result in nonunions and delayed bone healing (Park *et al.,* 2005; Lumawig *et al.,* 2009). NSAIDs are safe after spinal fusions and fracture fixation, according to other research, with little impact on bone-healing (Davis *et al.,* 1988). Glucocorticoids not only suppress osteoblast proliferation and function but also promote osteocyte apoptosis, leading to poor bone matrix formation and impaired mechanical strength. Antiresorptive agents like bisphosphonates, although beneficial in treating osteoporosis, may excessively suppress bone turnover when used long-term, potentially leading to brittle bones and delayed healing, especially in cases of atypical fractures. Moreover, chemotherapy drugs and radiation therapy can compromise bone vascularity and cellular viability, further hindering healing processes. These drug-induced alterations in bone quality and healing dynamics underscore the need for careful medication management in patients with fractures or those at high risk of skeletal injuries (Figure 6).

At-Risk Populations

Postmenopausal women and elderly individuals represent high-risk populations for adverse outcomes from bone-drug interactions due to their already compromised bone health. In postmenopausal women, the decline in estrogen levels accelerates bone resorption, making them more susceptible to drug-induced bone loss, especially when taking medications like glucocorticoids, aromatase inhibitors, or anticoagulants. Similarly, elderly individuals often have multiple comorbidities requiring polypharmacy, increasing the likelihood of exposure to drugs that negatively affect bone metabolism, such as proton pump inhibitors, antiepileptics, and SSRIs. The need of routine bone health monitoring and preventive measures in clinical care is highlighted by the fact that these individuals are especially susceptible to decreased bone mineral density, delayed fracture healing, and increased fracture risk (Yadalam *et al.*, 2025; García Rodríguez *et al.,* 2007). Cancer patients undergoing chemotherapy or Androgen Deprivation Therapy (ADT) are at a heightened risk for bone-drug interactions that can severely

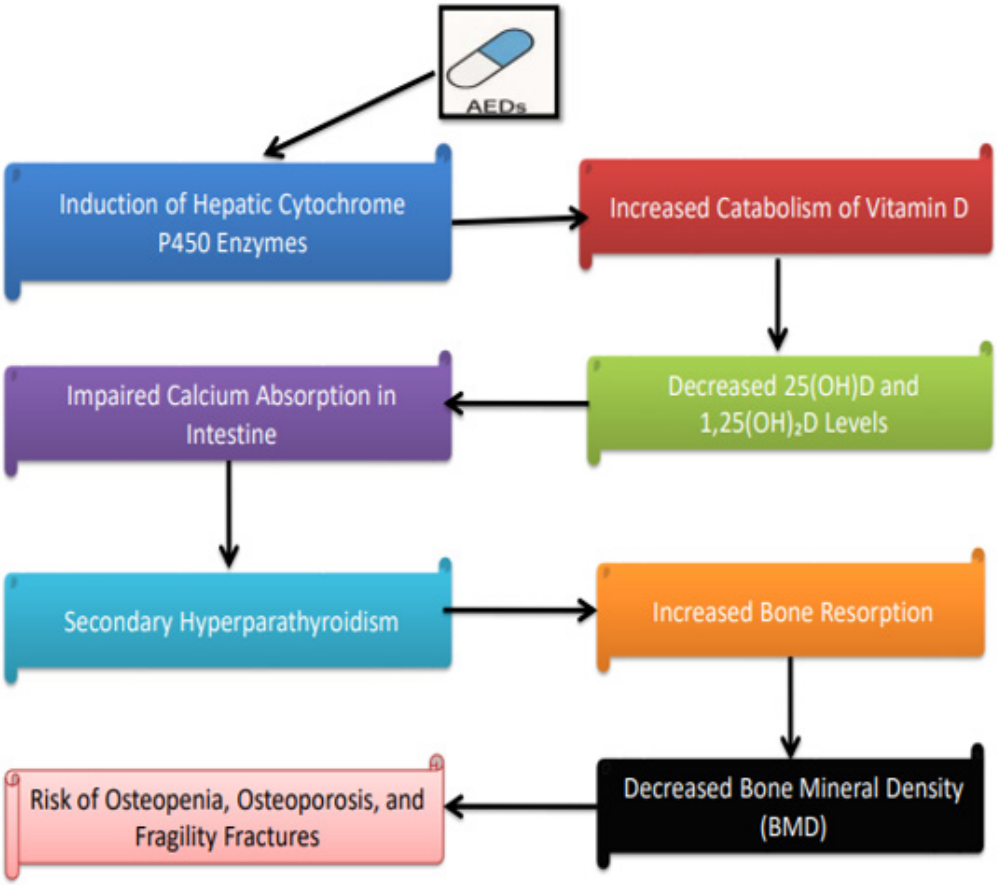

Figure 2: Mechanism of Antiepileptic Drug (AED)-Induced Bone Loss.

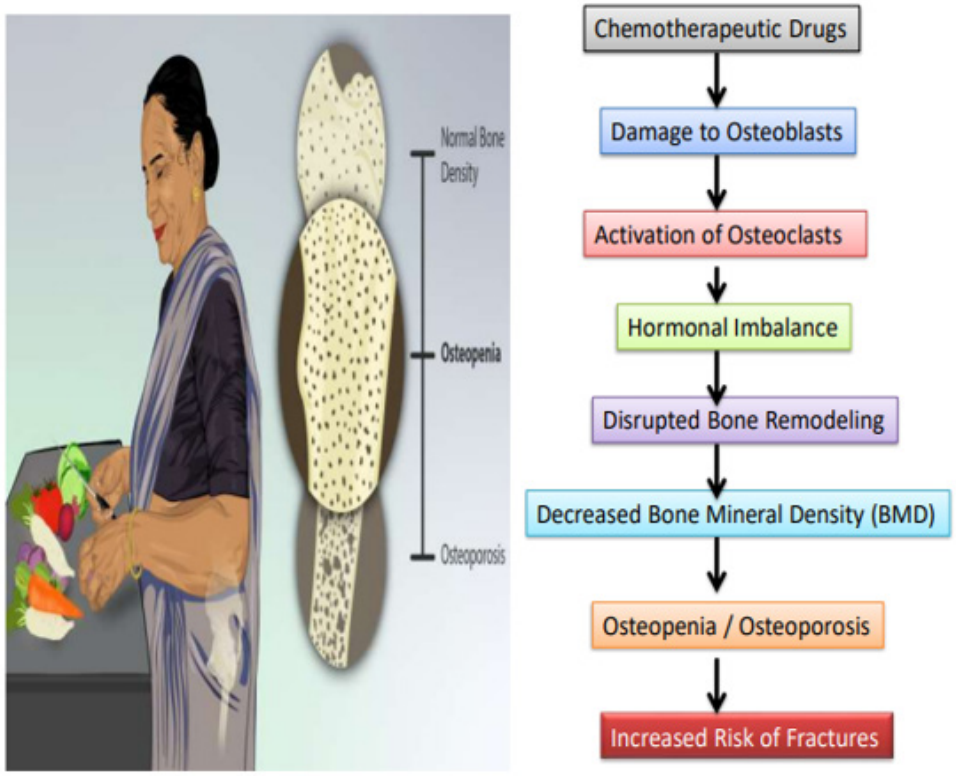

Figure 3: Impact of Chemotherapeutic Drugs on Bone Health.

impact skeletal health. Chemotherapeutic agents can impair bone remodeling by directly affecting osteoblast and osteoclast function, reducing bone formation and increasing resorption. The effects of ageing and androgen deprivation, which result in decreased muscle mass and function, increased fat, and decreased mobility, are additional factors that contribute to bone fragility. While ADT contributes to muscular dysfunction and muscle loss, testosterone is essential for maintaining muscle mass (Saad *et al.*, 2017). Lean body mass fell by 2.7% (p<0.001) in a trial of 32 evaluable patients treated with gonadotropic releasing hormone agonists over a 48-week period, whereas body mass index grew by 2.4% (p=0.005) (Smith *et al.*, 2002). Age-related muscular atrophy that is left untreated might increase the risk of fractures and falls. 5-13% of people over 65 have lost muscle mass, while for people over 80, the percentage rises to 50% (Padilla Colón *et al.*, 2018). Significant drops in testosterone levels are experienced by ADT users, especially those with prostate cancer, which accelerates bone loss and increases the risk of osteoporosis and fractures. Three primary factors influence the likelihood of fragility fractures in patients with prostate cancer: (1) ageing; (2) cancer treatment, particularly ADT; and (3) cancer phenotype. Peak BMD is often reached in young adulthood, usually around age 20. It is maintained until about age 40, after which it starts to drop as one age. Age-related increases in fracture risk are significant and beyond the effects of BMD loss (Khosla *et al.*, 2013). Variations among people with the same cancer diagnosis are referred to as cancer phenotypes. Additionally, certain cancer treatments may interfere with calcium and vitamin D metabolism or cause prolonged immobility, further compounding the risk of skeletal complications. These patients require proactive bone health assessment and management to prevent drug-induced bone deterioration and associated morbidities. Patients with chronic illnesses requiring long-term medication, such as epilepsy, acid reflux, or autoimmune disorders, are particularly vulnerable to bone-drug interactions that can compromise bone health (Moyad *et al.*, 2013). Antiepileptic drugs like phenytoin and carbamazepine can induce hepatic enzymes that accelerate vitamin D degradation, leading to decreased calcium absorption and increased bone resorption (Valsamis *et al.*, 2006). Similarly, prolonged use of proton pump inhibitors for acid reflux may reduce stomach acid levels, impairing calcium absorption and contributing to reduced bone mineral density. In autoimmune conditions, long-term corticosteroid therapy often essential for disease management can significantly impair osteoblast function and increase osteoclast activity, resulting in secondary osteoporosis (Martinis *et al.*, 2021). These patients face a heightened risk of fractures and delayed healing, making bone health monitoring and preventive interventions crucial components of their long-term care.

MANAGEMENT OF BONE-DRUG INTERACTIONS

Prevention Strategies

Nutritional Interventions

By promoting bone mineralisation and preventing drug-induced bone loss, adequate calcium and vitamin D supplementation

is essential for managing bone-drug interactions (Figure 7). Numerous drugs, including proton pump inhibitors, corticosteroids, and antiepileptics, can alter the metabolism of vitamin D or interfere with calcium absorption, which reduces bone density and increases the risk of fractures. Supplementation helps maintain optimal serum calcium levels and enhances calcium absorption in the gut, which is essential for preserving bone strength. Additionally, vitamin D supports osteoblast function and reduces Parathyroid Hormone (PTH)-mediated bone resorption. Physical exercise and getting the appropriate amounts of calcium and vitamin D during adolescence and early adulthood will guarantee the development of peak bone mass, which is typically reached by the age of 30 (IOM 1997). Numerous cell processes depend on calcium, which is a vital component of the human body. In addition to being vital for healthy bones, calcium is also necessary for blood coagulation, neuromuscular activity, and healthy heart function. It is essential to bone architecture and necessary for the lifelong deposition of bone mineral. Calcium is also present in the Extracellular Fluid (ECF), often known as plasma, even though the body stores over 99% of it in the bones and teeth. Calcium equilibrium is determined by plasma calcium levels. Bone resorption rises in order to raise plasma levels if they fall. To keep this balance, one must consume enough calcium. Vitamin D facilitates the absorption of calcium in the small intestine (FR *et al.*, 2008). Although there is some faecal loss, the kidneys are the main organs responsible for excreting calcium. An essential mineral for maintaining bone health is Vitamin D. Vitamin D is primarily responsible for controlling intestinal calcium absorption and promoting bone resorption, which maintains serum calcium levels (Reid, 2010). Vitamin D can be found in food, supplements, and sunlight. Most Americans don't get enough vitamin D in their bodies. Actually, 90% of persons between the ages of 51 and 70 are thought to be deficient in vitamin D from their diet (Moore *et al.,* 2004). The 7-dehydrocholesterol found in the skin absorbs Ultraviolet B (UVB) rays from sunlight to create previtamin D3. Heat rapidly transforms the unstable substance previtamin D3 into vitamin D3 (MacLaughlin *et al.,* 1982). Vitamin D-Binding Protein (DBP) pulls vitamin D3 into the capillaries from the extracellular space. Vitamin D is sent to the liver from the capillaries, where it is hydroxylated to create 25-hydroxyvitamin D [25(OH)D]. After being bound by DBP once more, 25-hydroxyvitamin D is transported to the kidney, where it is liberated into the renal tubule cell and hydroxylated to create 1,25-dihydroxyvitamin

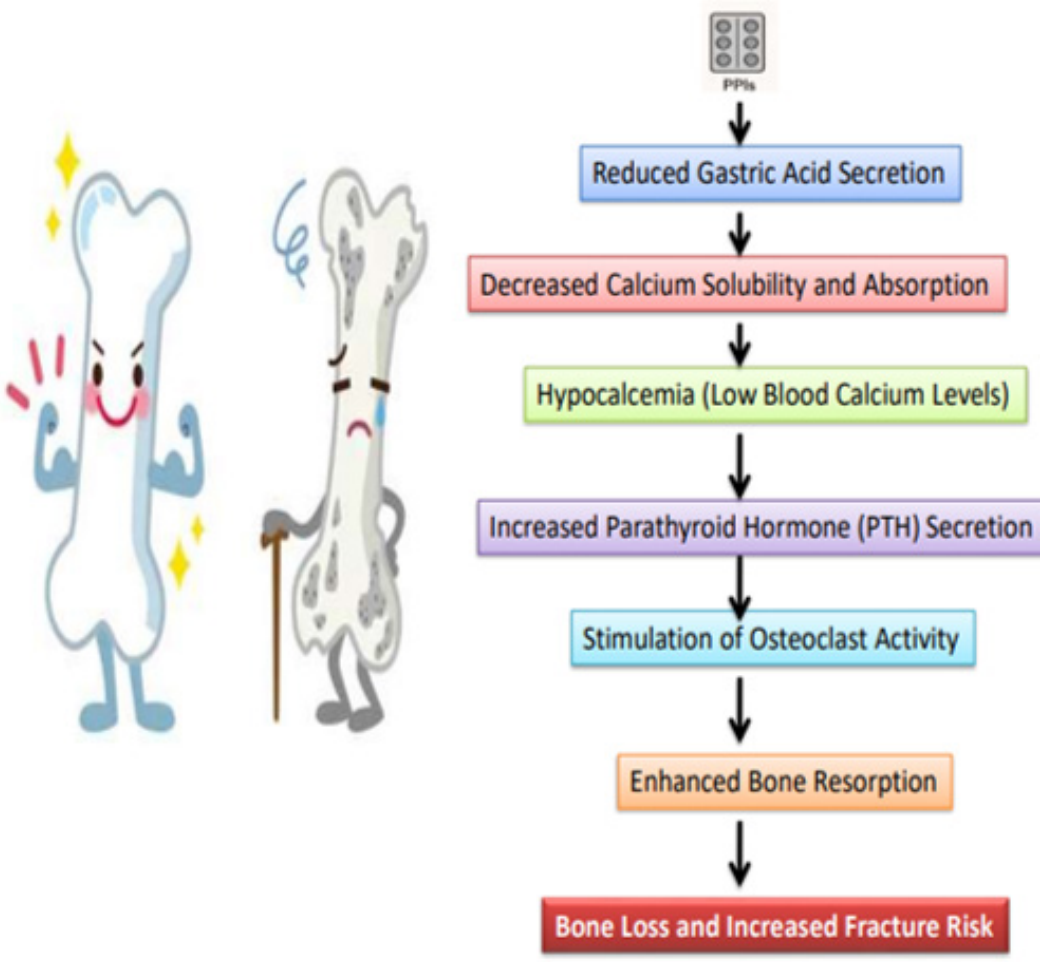

Figure 4: Proton Pump Inhibitor (PPI)-Induced Bone Loss Mechanism.

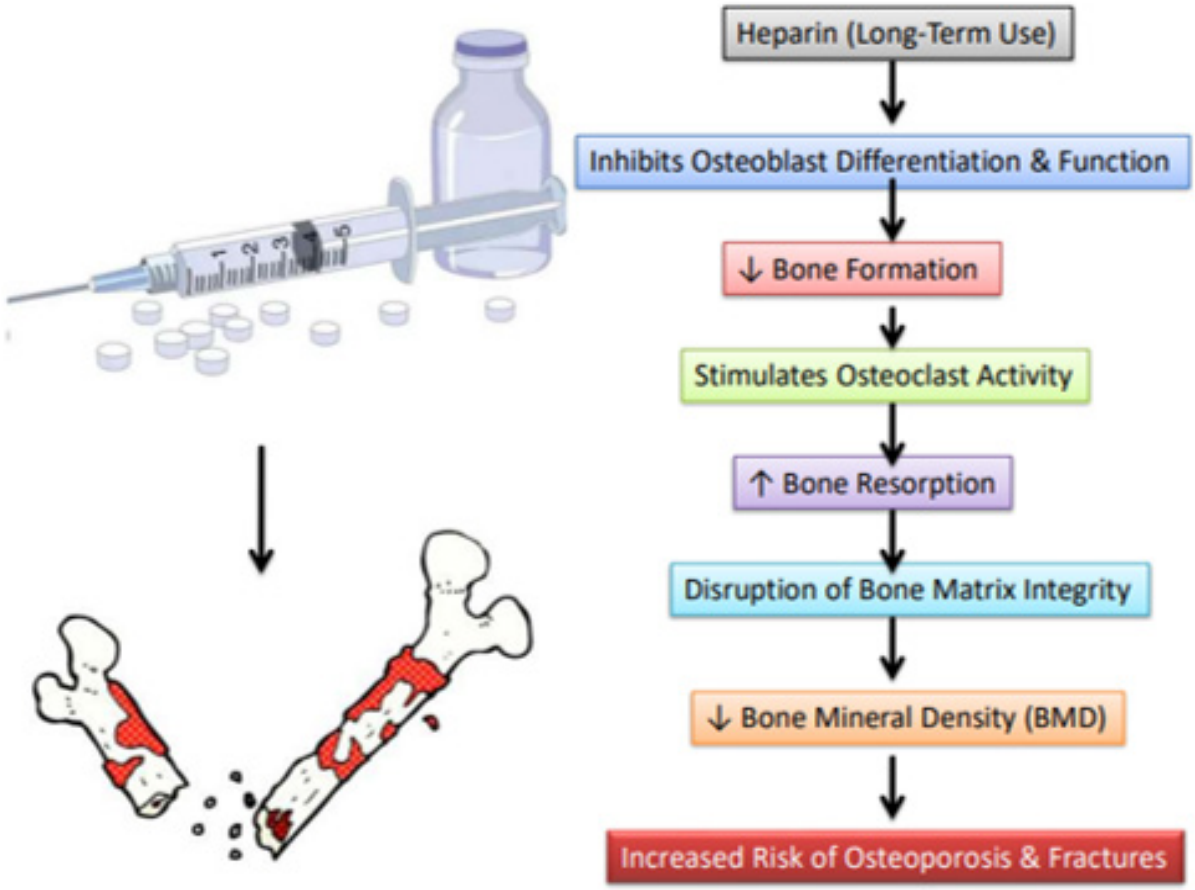

Figure 5: Mechanism of Heparin-Induced Bone Loss.

D [1,25(OH)2D] (DeLuca *et al.,* 2004). Calcium homeostasis is maintained by this physiologically active form of vitamin D. Ensuring sufficient intake of these nutrients is especially important for at-risk populations, including postmenopausal women, the elderly, and patients on long-term pharmacotherapy, as part of a comprehensive bone health strategy.

Lifestyle Modifications

Non-pharmacological methods such as regular weight-bearing exercises and quitting alcohol and tobacco are essential for maintaining bone health, particularly in patients with bone-drug interactions. Exercise increases muscle strength and balance, transfers loads to the skeleton, and may lower the incidence of fractures and falls (Schwarz *et al.,* 2004). Except for a few non-weight-bearing activities, like swimming, it is widely accepted that a high level of activity equates to a high amount of mechanical stress. A positive impact in this age range is supported by several research conducted in children and young adults (Detter *et al.,* 2014). Long-term statistics are a little more scarce among adults. There aren't many long-term prospective studies that we are aware of physical activity decreases forearm bone loss in postmenopausal women, according to a 25-year prospective research (Kelley *et al.,* 2013). However, there is mounting evidence particularly from meta-analyses that physical activity during adulthood can reduce the incidence of fractures and preserve Bone Mineral Density (BMD). Premenopausal women's overall risk of total fractures was significantly inversely correlated with this, according to a meta-analysis (Kelley *et al.,* 2000). The results from a number of previous meta-analyses in both men and women are supported and expanded upon by this (Wong *et al.,* 2007). Exercises including weight bearing and resistance training increase bone production, boost osteoblast activity, and preserve or increase bone mineral density, all of which lower the risk of fractures. However, one of the most significant lifestyle variables that lowers bone mass is smoking. Naturally, it is a modifiable risk factor that needs to be included when determining a person's risk of fracture (Yoon et al., 2012). It has been demonstrated that smoking causes changes in the metabolism of calciotropic and adrenal cortical hormones, which further increases bone resorption (Steptoe *et al.,* 2006). Smoking has been linked to elevated cortisol levels in clinical investigations (Canalis *et al.,* 2007). Excess glucocorticoids change osteoblastic and osteoclastic activity, which has a direct and indirect impact on bone remodeling (Maurel *et al.,* 2012). While excessive alcohol use disrupts bone remodelling and raises the risk of falls and fractures, it has been demonstrated to reduce bone mass and limit calcium

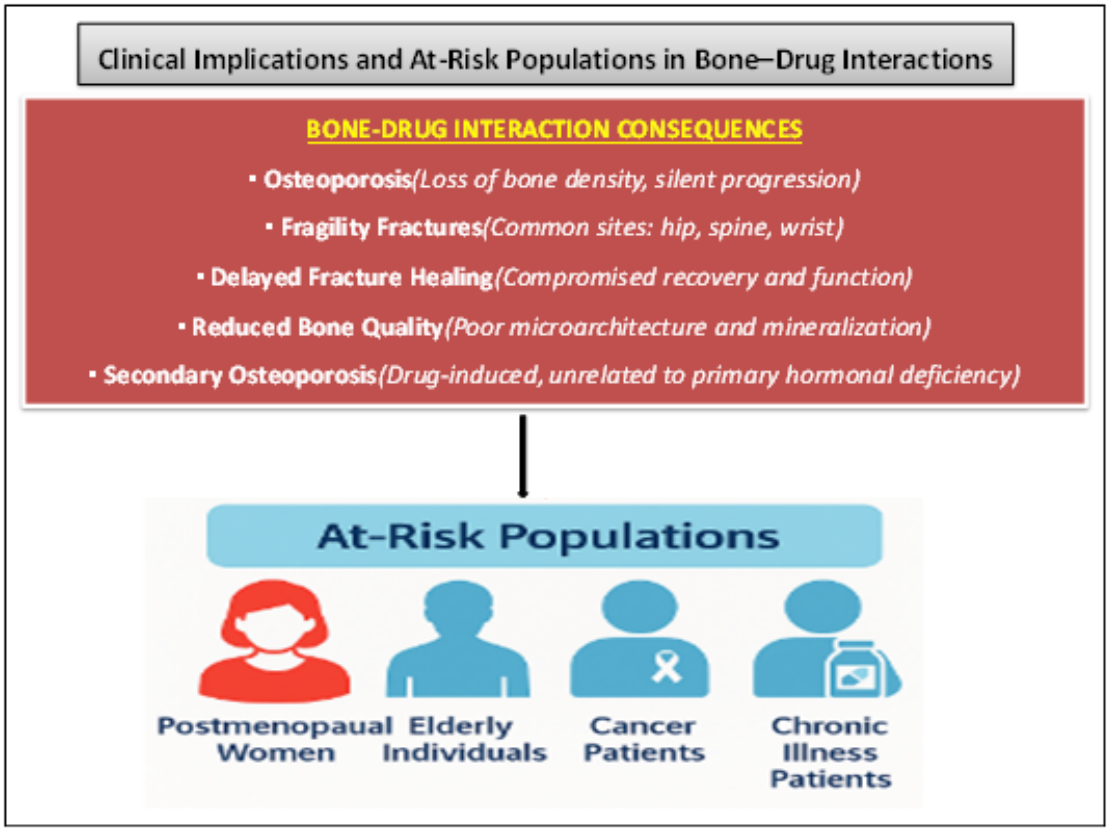

Figure 6: Clinical Implications and At-Risk Populations.

absorption. Both direct, endocrine, metabolic, and nutritional actions that converge on the bone modulate the impact of alcohol use on the risk of osteoporotic fractures. A higher risk of falling as a result of intoxication and/or neuropathy exacerbates the effects of skeletal fragility in a subgroup of individuals (Cawthon *et al.,* 2006). Alcohol has complicated and dose-dependent effects on sex steroids. Light or moderate alcohol usage can be linked to a delayed menopause (Sapre *et al.,* 2014) and higher serum free testosterone following menopause (Rinaldi *et al.,* 2006), despite the fact that long-term, severe alcohol use can lower levels of free testosterone and oestradiol. Chronic high consumption can also result in hypercortisol and a decrease in serum leptin (Besemer *et al.,* 2011). Poor nutrition, exocrine pancreatic insufficiency with malabsorption, and vitamin D inadequacy can all coexist with alcoholism. Studies have repeatedly indicated that moderate or high alcohol consumption increases the incidence of fractures in both men and women (Johnell *et al.,* 1985), even if the effects of low to moderate alcohol consumption on BMD appear to be somewhat beneficial (Kanis *et al.,* 2005). Lifestyle modifications, including regular physical activity and avoiding tobacco and alcohol, are essential components of a holistic approach to preserving skeletal health and mitigating the adverse effects of medications on bone.

Medication Review

Assessment of polypharmacy in elderly patients is a critical component in the management of bone health, as multiple medications can have cumulative or synergistic effects that negatively impact bone metabolism. Elderly individuals are often prescribed several drugs for chronic conditions, increasing the risk of bone-drug interactions, such as those involving corticosteroids, proton pump inhibitors, anticoagulants, and psychotropic medications. Regular medication reviews help identify agents that contribute to bone loss or fall risk and allow for dose adjustments, substitution with bone-friendly alternatives, or discontinuation of unnecessary drugs (Hoel *et al.,* 2021). This careful evaluation not only helps prevent drug-induced osteoporosis and fractures but also promotes safer and more effective treatment outcomes in geriatric care.

Pharmacological Interventions

The use of bisphosphonates and denosumab is a key pharmacological intervention for managing bone loss in patients receiving glucocorticoids or chemotherapeutic agents (Coskun Benlidayi, 2018). Many common medical disorders, such as rheumatoid arthritis, asthma, and chronic obstructive pulmonary disease, are treated with glucocorticoids. The primary cause of both drug-induced osteoporosis and secondary osteoporosis has been the use of glucocorticoids (Buckley *et al.,* 2018). 30-50% of patients experienced bone fractures as a result of long-term glucocorticoid

usage (Staa *et al.,* 2002). It is crucial to stop people who have used steroids for a long time from developing Glucocorticoid-Induced Osteoporosis (GIO). The most widely utilised medications for the treatment of GIO at the moment are bisphosphonates (Reid *et al.,* 2009). By inhibiting osteolysis, oral bisphosphonates have been shown to effectively prevent Bone Mineral Density (BMD) loss in GIO patients (Saag *et al.,* 1998). Rapid bone density loss and an increased risk of fracture result from glucocorticoids' large increases in bone resorption and decreases in bone production. The most widely utilised medications for the treatment of GIO at the moment are bisphosphonates (Nasomyont *et al.,* 2021). By inhibiting osteolysis, oral bisphosphonates have been shown to effectively prevent Bone Mineral Density (BMD) loss in GIO patients (Adachi *et al.,* 2001). Inhibiting osteoclast-mediated bone resorption, bisphosphonates (such as alendronate, risedronate, and zoledronate) are frequently recommended to prevent and treat osteoporosis brought on by glucocorticoids. Alternatively, GIO patients have shown success with denosumab. Every six months, 60 mg of denosumab was administered subcutaneously. Denosumab has been shown to efficiently raise BMD without causing therapeutic plateaus, and it has also been linked to fewer acute-phase responses and renal impairments (Leipe *et al.,* 2021). Denosumab, a monoclonal antibody that inhibits RANKL, also effectively reduces bone resorption and is particularly beneficial in cancer patients undergoing androgen deprivation therapy or chemotherapy, where bone loss is often severe. Both agents have demonstrated efficacy in preserving bone mineral density, reducing fracture risk, and providing skeletal protection in high-risk patient populations undergoing long-term pharmacotherapy. Prescribing Selective Estrogen Receptor Modulators (SERMs) or Hormone Replacement Therapy (HRT) is an important pharmacological intervention for controlling bone health in postmenopausal women, who are at increased risk of osteoporosis due to estrogen insufficiency. SERMs, such as raloxifene, replicate the positive effects of estrogen on bone by lowering bone resorption and enhancing bone mineral density without activating breast or uterine tissue (Devaraji *et al*., 2025). HRT, which involves the administration of estrogen alone or in

Figure 7: Management and Future Directions.

combination with progesterone, effectively prevents bone loss and reduces fracture risk when initiated around the time of menopause. However, HRT is generally reserved for women with significant menopausal symptoms and without contraindications, due to potential risks such as thromboembolism and breast cancer (Bartl *et al.,* 2023). Both SERMs and HRT should be considered carefully based on individual risk profiles, and their use should be part of a comprehensive strategy for bone preservation in postmenopausal women. When patients are using Proton Pump Inhibitors (PPIs) or Antiepileptic Medications (AEDs), which can both have a detrimental effect on bone health, coadministration of supplements like calcium and vitamin D is a crucial pharmacological intervention (Koyyada, A., 2021). PPIs reduce gastric acid secretion, impairing calcium absorption especially from calcium carbonate leading to decreased bone mineral density over time. Similarly, long-term use of AEDs like phenytoin and carbamazepine induces hepatic enzymes that accelerate the breakdown of vitamin D, resulting in calcium deficiency and increased bone resorption. To counteract these effects, supplementation with calcium (preferably calcium citrate, which does not require acidic conditions for absorption) and vitamin D helps maintain adequate serum calcium levels and supports bone mineralization (Vestergaard, 2020). In order to minimise drug-induced bone loss and lower the risk of fractures in these patients, regular monitoring and supplements are essential.

Monitoring and Surveillance

In order to manage bone health, routine Bone Mineral Density (BMD) testing is an essential diagnostic and monitoring tool, especially for high-risk groups including postmenopausal women, the elderly, and patients using long-term drugs like glucocorticoids, PPIs, or antiepileptics. In older adults, repeating Bone Mineral Density (BMD) testing after four years provided minimal improvement in predicting hip and major osteoporotic fractures compared to a single baseline BMD measurement. This suggests that routine repeat BMD testing within short intervals may have limited clinical benefit in untreated individuals (Berry *et al.,* 2013). Early identification of osteopenia or osteoporosis before fractures develop is made possible by BMD testing, which is usually carried out using Dual-Energy X-ray Absorptiometry (DEXA). It also helps clinicians assess the effectiveness of treatment interventions and make informed decisions regarding the initiation or adjustment of pharmacological therapies. Routine BMD evaluations ensure timely identification of bone loss, enabling targeted prevention strategies and reducing the risk of fractures and associated complications. A useful technique for managing bone health is the use of biochemical markers for bone turnover, particularly for evaluating fracture risk and tracking how well osteoporosis medications are working (Delmas *et al.,* 2000). The dynamic process of bone remodelling is reflected by these indicators, which include those for bone resorption (e.g., serum C-Terminal Telopeptide [CTX], urine N-Terminal Telopeptide [NTX]) and bone production (e.g., serum osteocalcin, bone-specific alkaline phosphatase) (Ebeling, 2024). Changes in these markers can provide early indications of treatment response before changes in bone mineral density become apparent. They are particularly useful in evaluating adherence to therapy and tailoring treatment strategies, making them an important adjunct to imaging-based assessments in the comprehensive management of bone disorders.

RESEARCH DIRECTIONS

Future research in the field of bone-drug interactions is advancing toward precision-targeted interventions and improved therapeutic safety. A central focus is on the development and clinical application of emerging therapies that target specific molecular pathways involved in bone remodeling. In high-risk groups, such as cancer patients receiving androgen deprivation therapy, RANKL inhibitors, like denosumab, have shown notable effectiveness in stopping bone resorption and lowering the incidence of fractures (Leipe *et al.,* 2021). Ongoing studies are also investigating agents that modulate Wnt signaling, sclerostin inhibitors, and cathepsin K inhibitors, all of which aim to selectively enhance bone formation or inhibit resorption with minimal off-target effects (Xu *et al.,* 2023). Another critical area of research involves the development of safer drug formulations. This includes modifying existing drugs to reduce their adverse effects on bone such as glucocorticoids with lower osteotoxic profiles and designing drug delivery systems that minimize systemic exposure. Nanotechnology and bone-targeted drug carriers are promising innovations that may allow localized treatment of disease without compromising skeletal integrity. Additionally, personalized medicine is becoming increasingly important in the management of bone-drug interactions. Advances in pharmacogenomics, biomarker profiling, and risk stratification tools can help identify individuals who are genetically or physiologically predisposed to drug-induced bone loss (Deivayanai *et al*., 2024). This would enable clinicians to tailor therapies, adjust dosages, and implement early preventive strategies such as supplementation or concurrent bone-protective agents. Research is also needed to integrate electronic health records and decision-support tools to flag potential bone-related drug risks in polypharmacy settings, especially among elderly and chronically ill patients. Overall, these research directions aim not only to prevent and manage bone-drug interactions more effectively but also to enhance therapeutic outcomes and quality of life for at-risk populations.

CONCLUSION

Bone-drug interactions can lead to significant bone loss and fractures, particularly in high-risk populations. Early detection through BMD testing and biochemical markers, alongside preventive strategies like supplementation and lifestyle changes,

are essential for managing these risks. A multidisciplinary approach is key, involving clinicians, pharmacists, and specialists to ensure effective bone health management. Ongoing research into safer therapies and personalized treatments will further enhance the care of patients affected by bone-drug interactions.

ACKNOWLEDGEMENT

The authors express they're thanks to Saveetha College of Pharmacy - SIMATS for providing the necessary facilities to carry out this research work.

ABBREVIATIONS

BMD: Bone Mineral Density; **PPI:** Proton Pump Inhibitor; **AED:** Antiepileptic Drug; **GC:** Glucocorticoid; **RANKL:** Receptor Activator of Nuclear Factor Kappa-B Ligand; **SERM:** Selective Estrogen Receptor Modulator; **HRT:** Hormone Replacement Therapy; **CTX-C:** terminal Telopeptide (a bone resorption marker); **OC:** Osteocalcin (a bone formation marker); **DEXA:** Dual-Energy X-ray Absorptiometry.

FUNDING SOURCES

The author(s) received no financial support for the research, authorship, and/or publication of this article.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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Cite this article: Pandi K, Cheriyan BV, Murali D, Boobalan N, Harikrishnan J, Kannan D, *et al*. Medications and Bone Health: A Comprehensive Review of Skeletal Risks and Therapeutic Approaches. Int. J. Pharm. Investigation. 2026;16(3):843-58.