Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Review Article

J Exp Clin Med
2025; 42(3): 324-337
doi: 10.52142/omujecm.42.3.16

Effects of sertraline use on bone microarchitecture: A literature review

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Received: 24.05.2025 • **Accepted/Published Online:** 16.07.2025 • **Final Version:** 30.09.2025

Abstract

Selective serotonin reuptake inhibitors (SSRIs), particularly sertraline, are widely prescribed for depression and anxiety disorders. Although primarily targeting the central nervous system, emerging evidence suggests that SSRIs can significantly impact bone health. This narrative review aims to evaluate the clinical effects of long term SSRI use on bone mineral density (BMD) and fracture risk. A literature review was conducted across PubMed, Scopus, Web of Science, and Google Scholar, covering studies from 1998 to 2025. Results from both preclinical and clinical data consistently demonstrate a reduction in BMD associated with prolonged SSRI exposure, particularly in trabecular rich anatomical regions such as the femoral neck, vertebrae, and mandible. These changes have been linked to decreased osteoblastic activity and increased bone resorption, leading to structural weakening and elevated fracture risk. Clinical findings suggest that elderly individuals and postmenopausal women are especially vulnerable, and that fracture risk appears to correlate with both the dose and duration of SSRI therapy. While the exact molecular mechanisms remain under investigation, the clinical implications are clear: bone health assessment and monitoring should be integral to the care of patients prescribed SSRIs, particularly those with additional risk factors for osteoporosis. Interventions such as BMD screening, calcium and vitamin D supplementation, and lifestyle modifications may be beneficial in reducing skeletal complications. This review underscores the need for increased clinical awareness and interdisciplinary management strategies to mitigate potential bone-related side effects of SSRI treatment in at risk populations.

Keywords: sertraline, selective serotonin reuptake inhibitors, bone mineral density, osteoporosis risk, fracture, bone health

1. Introduction

Selective serotonin reuptake inhibitors (SSRIs) are among the most frequently prescribed medications for major depressive disorder, anxiety disorders, obsessive-compulsive disorder, and panic disorder (1). Sertraline, a leading SSRI, is widely used due to its clinical efficacy and relatively tolerable side effect profile. While SSRIs' central nervous system actions are well known, recent studies highlight their significant peripheral effects, particularly on skeletal tissues (2, 3).

Clinical and epidemiological evidence has demonstrated that long-term SSRI use, especially in postmenopausal women and older adults, is associated with reduced in bone mineral density (BMD) and increased risk of osteoporotic fractures (4, 5). The serotonin system's role in bone metabolism is dual: Centrally derived serotonin promotes osteoblast activity, while peripheral serotonin (mainly from the gut) inhibits osteoblasts and stimulates osteoclastogenesis, promoting bone resorption (6). Animal models have confirmed that sertraline inhibits osteoblast proliferation and impairs bone matrix mineralization (7, 8). Moreover, bone structures with high trabecular content and active remodeling (e.g., femoral neck, vertebrae, mandible) are especially susceptible to these changes (9). This narrative review explores sertraline's impact on bone microarchitecture from molecular, cellular, and anatomical standpoints. We synthesize evidence from preclinical and clinical studies to examine bone histology, biomechanical alterations, and microstructural consequences of SSRI use. Additionally, the review outlines knowledge gaps and future research needs, urging that bone health should be a routine consideration in long-term SSRI therapy.

2. Literature Review Method

A structured and methodologically rigorous literature review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The objective was to identify and synthesize evidence on the effects of sertraline and other SSRIs on bone microarchitecture, encompassing both preclinical and clinical studies. Searches were conducted in PubMed, Scopus, Web of Science, and Google Scholar databases, covering literature published between January 1998 and February 2025. The search strategy employed a combination of controlled vocabulary (MeSH terms) and free-text keywords, including: "sertraline," "SSRI," "bone metabolism," "bone mineral density," "osteoblast," "osteoclast," "fracture risk," "Wnt signaling," "RANKL/OPG," "mandible," "femur," "vertebra," and "histomorphometry." Boolean operators ("AND," "OR") were applied to optimize search sensitivity and specificity. All

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identified records were managed using reference management software (e.g., EndNote), and duplicates were automatically removed. The screening process involved two independent reviewers who first assessed titles and abstracts, followed by full-text evaluations for methodological quality and relevance. Disagreements were resolved through discussion or a third reviewer. The inclusion criteria comprised original peer-reviewed studies, including animal models, in vitro research, and clinical trials published in English or Turkish. Case reports, conference abstracts, editorials, and grey literature were excluded to maintain methodological rigor.

The literature analyzed spanned a 27-year publication range, from 1998 to 2025, ensuring both historical depth and contemporary relevance. The selection process is detailed in the Fig. 1, which transparently documents each stage of study identification, screening, eligibility, and inclusion.

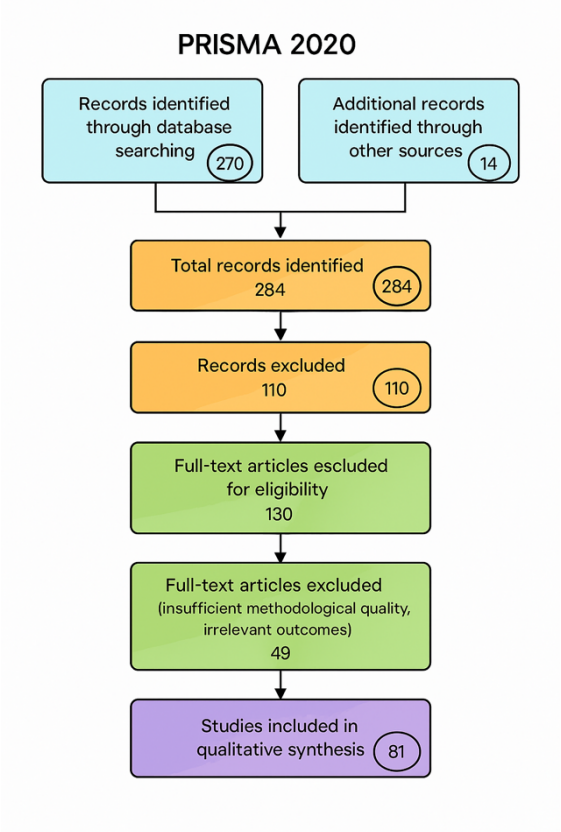

Fig. 1. Article selection according to PRISMA criteria

The review includes animal experiments, clinical studies, systematic reviews, and preclinical research published between 1998 and 2025. Only studies published in peer-reviewed journals in English and Turkish were included. Case reports and editorial articles were set as exclusion criteria. The content of the selected studies was assessed based on methodological quality, sample size, and the manner in which findings were reported, studies meeting these criteria were included in the review. This approach aims to provide a comprehensive perspective on the topic within a multidisciplinary framework.

3. Mechanism and Systemic Effects of Sertraline

Sertraline exerts its therapeutic effect by inhibiting the reuptake of serotonin (5-hydroxytryptamine, 5-HT) from presynaptic neurons. As a result, the level of serotonin in the synaptic cleft increases, leading to enhanced postsynaptic serotonergic transmission (10). Serotonin functions not only as a neurotransmitter in the central nervous system but also as plays a regulatory role in many peripheral systems. The effects of SSRIs can lead to physiological changes in various peripheral tissues where serotonin transporters (SERT) and receptors are present, including the gastrointestinal system, cardiovascular system, endocrine structures, and skeletal system (11, 12).

The systemic effects of sertraline, especially as revealed by recent studies, suggest that it may have potential consequences not only in neuropsychiatric domains but also in areas such as bone metabolism, connective tissue, and the gut-hormone axis (2). Therefore, it is highlighted that SSRI therapy should not be limited to neurological targets alone but must also be investigated in relation to peripheral organ systems.

3.1. Serotonin and Bone Metabolism

Serotonin functions not only as a neurotransmitter in the central nervous system but also as an important regulatory agent in bone metabolism. It exerts these effects through two primary sources of production: central serotonin (synthesized in the brain) promotes bone formation by supporting osteoblastic activity, while peripheral serotonin (mainly released from enterochromaffin cells) when entering the circulation, inhibits osteoblast proliferation and negatively affects bone formation (12, 13).

The inhibition of serotonin reuptake by SSRIs may lead to increased peripheral serotonin levels. This condition can result in decreased BMD through mechanisms such as the suppression of osteoblast functions and the enhancement of osteoclastic activity, which together disrupt the balance between bone formation and resorption (2, 14). Long-term use of SSRIs has been shown to reinforce this effect in both preclinical animal models and clinical populations (7, 13).

3.2. Balancing Osteoblast and Osteoclast Activity

Bone tissue is maintained through a dynamic remodeling process that continues throughout life, regulated by the cellular balance between osteoblasts and osteoclasts. This balance is achieved by the simultaneous continuation of bone formation by osteoblasts and bone resorption by osteoclasts. SSRIs, particularly agents like sertraline, can exert various biological effects on these cell groups. Sertraline has been shown to inhibit the proliferation and differentiation of osteoblasts, with some studies suggesting that this inhibition occurs through apoptotic mechanisms (14). On the other hand, increased serotonin levels have been shown to enhance osteoclast activity, thereby accelerating the bone resorption process (10). These mechanisms lead to decreased bone matrix synthesis and impaired mineral density.

Preclinical animal studies have reported that long-term sertraline administration results in reduced trabecular bone

density and overall bone volume (12). These findings suggest that SSRIs may disrupt bone tissue homeostasis and contribute to osteopenic and osteoporotic processes.

3.3. Interactions with Hormones

SSRIs can cause significant changes in bone metabolism not only by altering neurotransmitter levels but also by indirectly affecting certain hormonal systems. They have been shown to influence the hypothalamic-pituitary-adrenal (HPA) axis, thereby altering cortisol levels. Elevated cortisol suppresses osteoblast activity and reduces bone formation, while enhancing osteoclastic activity, thus promoting bone resorption. Over time, this can lead to a decrease in BMD and an increased risk of osteoporosis (15, 16).

Additionally, SSRIs are believed to have indirect effects on estrogen signaling. Estrogen is a key hormone in maintaining the homeostatic balance of bone tissue. Particularly in the postmenopausal period, the natural decline in estrogen levels combined with potential SSRI interference in this signaling pathway may accelerate bone loss (17). Therefore, it is clinically important to monitor BMD and implement bone health measures in postmenopausal women receiving SSRI therapy.

3.4. Serotonin Transporter and Bone Cells

The serotonin transporter protein (SERT or 5-HTT), responsible for serotonin reuptake, is found not only in nerve cells but also in bone cells such as osteoblasts, osteocytes, and osteoclasts. The expression of this transporter in bone cells indicates that serotonin signaling plays a significant role in bone metabolism (3, 18). By inhibiting SERT, SSRIs block serotonin reuptake, which can lead to elevated serotonin levels in bone cells. Studies have shown that SSRIs inhibit the proliferation and mineralization of osteoblasts while enhancing the differentiation and resorptive activity of osteoclasts (3). These effects disrupt bone homeostasis and may result in a long-term decrease in bone mineral density. Specifically, SSRIs like sertraline have been reported to accelerate bone resorption by reducing SERT expression in osteoclasts (19).

4. Morphological Changes in Bone Tissue

The effects of sertraline on bone tissue extend beyond cellular or molecular levels and manifest as macroscopic and microscopic changes in bone morphology. Particularly with long-term SSRI use, significant alterations may occur in both trabecular and cortical bone structures. These morphological changes have been demonstrated through various imaging techniques, histological evaluations, and animal models (6).

4.1. Effects on Trabecular and Cortical Bone Structure

Trabecular bone, due to its high metabolic activity and large surface area, is particularly sensitive to pharmacological interventions. As a result, disruptions in bone microarchitecture caused by changes in serotonin levels often manifest first in trabecular regions. Clinical and preclinical studies in SSRI users have reported structural alterations such as decreased trabecular thickness, reduced trabecular number, and expanded trabecular spaces (12, 20).

Animal model studies involving sertraline have observed a decrease in bone volume/total volume (BV/TV) ratio, trabecular thickness (Tb.Th), and trabecular number (Tb.N), along with an increase in trabecular separation (Tb.Sp) (2). These changes result in weakened bone microarchitecture and decreased mechanical strength.

Additionally, in cortical bone tissue, sertraline use has been associated with pathological changes including microstructural thinning, loss of compactness, and the formation of microfractures. These effects are particularly prominent in weight-bearing anatomical regions such as the femoral neck and vertebral column. In these regions, a reduction in BMD significantly increases fracture risk in individuals using SSRIs (4, 13).

4.2. Changes in Bone Density and Microarchitecture

The structural integrity of bone tissue should be assessed not only through BMD values but also by evaluating the overall quality of trabecular and cortical bone architecture. Microarchitecture is a critical determinant of bone strength, and disruptions in this network can significantly impair mechanical competence. Among selective SSRIs, sertraline has been shown in multiple preclinical models to negatively impact bone microstructure and overall bone quality (9). Experimental studies employing micro-computed tomography (micro-CT) and histomorphometric analysis have consistently demonstrated that sertraline exposure leads to a reduction in BV/TV, Tb.Th, and Tb.N. Conversely, there is a notable increase in Tb.Sp and structure model index (SMI), reflecting a transition from plate-like to rod-like trabecular geometry. This architectural deterioration is strongly associated with decreased mechanical resistance and compromised structural integrity (13, 21, 22). Such morphological changes are particularly detrimental in weight-bearing skeletal regions, where they predispose bone to microdamage accumulation and elevate the risk of clinical fractures. Taken together, these findings suggest that sertraline may impair bone health not merely through changes in density but via fundamental alterations in bone architecture.

4.3. Histological Findings

The effects of SSRIs like sertraline on bone tissue are clearly observable at the histological level. Histopathological examinations conducted on animal models treated with SSRIs have reported significant decreases in osteoblast numbers, increased osteoclast activity, and irregularities in bone surface morphology (23). In parallel with these cellular changes, bone matrix synthesis is slowed and the mineralization process is disrupted (24). This negatively affects both the quantity and quality of new bone formation. Additionally, increased fibrosis and adipogenesis have been observed in bone marrow cavities. These changes impair the functional structure of the bone marrow microenvironment, disrupting the balance between hematopoiesis and osteogenesis (12).

These findings have been confirmed not only through classical histological analyses using hematoxylin-eosin staining but also with immunohistochemical markers specific to osteoblast and osteoclast activity. A decrease in osteoblast markers such as RUNX2, osteocalcin, and alkaline phosphatase, along with an increase in osteoclast markers like TRAP and cathepsin K, has been observed (25, 26). These results suggest that SSRIs disrupt bone homeostasis at the molecular level by promoting resorptive processes.

4.4. Bone Mineral Density Findings

The impact of sertraline on bone mineral density has also been demonstrated in human clinical settings through imaging methods such as DEXA (Dual-energy X-ray Absorptiometry). In individuals using SSRIs, significant reductions in BMD have been reported, particularly in regions like the femoral neck, lumbar vertebrae, and radius (4, 27). Some studies indicate that this reduction ranges between 3 and 6%, while long-term use can lead to decreases of up to 10%. This decline becomes more pronounced in elderly individuals and postmenopausal women, significantly increasing the risk of fractures (16, 28).

5. Fracture Risk and Clinical Findings in Sertraline Use

SSRIs, especially sertraline, not only affect neurotransmitter levels but also impact bone metabolism, leading to reductions in BMD and an increased risk of fractures. This effect is associated not only with the pharmacological actions on osteoblast and osteoclast cells but also with neurological and musculoskeletal complications that may arise due to SSRI use (29).

Clinical studies have shown that individuals using SSRIs particularly elderly adults and postmenopausal women exhibit significant reductions in BMD, which in turn increases the risk of osteoporotic fractures. Long-term use of SSRIs like sertraline has been found to suppress osteoblast activity and increase osteoclastic activity, thus negatively affecting bone formation and weakening bone tissue (5, 30). These findings suggest that long-term use of SSRIs such as sertraline may increase the risk of osteoporosis and fractures, particularly in elderly individuals. Therefore, it is clinically important to regularly monitor bone health and implement preventive measures in patients who are planning to start or are already undergoing SSRI treatment.

5.1. Retrospective Clinical Studies

SSRIs, especially sertraline, may have adverse effects on BMD, thereby increasing fracture risk. This effect stems not only from the direct pharmacological impact on bone cells but also from SSRI-related neurological and musculoskeletal complications.

A comprehensive meta-analysis published in 2024 reported that SSRI use may increase the risk of hip fractures by 2.5 times. This study found that the decline in BMD was significantly associated with both the duration and dosage of sertraline use, thereby substantially influenced fracture incidence. Moreover, SSRI use for one year or longer was strongly correlated with a marked decline in BMD, and fracture risk increases were often dose and duration dependent. Some studies have indicated that SSRIs such as sertraline are associated with rapid BMD loss, particularly observed in areas like the femoral neck and vertebral column (31).

These findings highlight the negative effects of SSRI use on bone health and indicate that special attention should be given to bone status, particularly in elderly individuals, when planning SSRI treatment.

5.2. Risk Analysis in Postmenopausal Women and Elderly Individuals

Postmenopausal women are already at high risk for osteoporotic fractures due to estrogen deficiency related bone loss. SSRI use further increases fracture risk in this population. The combined effect of decreased estrogen and SSRI use synergistically suppresses bone formation and accelerates resorption (32). In elderly individuals, the use of SSRI combined with age-related muscle weakness, balance impairment, and osteopenia presents a serious risk of fracture related to falls (33). Studies report that fracture rates among women over 65 using SSRIs can be up to twice as high as control groups (34).

5.3. Vitamin D, Calcium Deficiency, and the SSRI Connection

The negative effects of SSRIs, particularly sertraline, on bone metabolism may be significantly exacerbated by coexisting deficiencies in vitamin D and calcium. Vitamin D plays a critical role in maintaining bone mineralization by enhancing intestinal calcium absorption and promoting osteoblastic activity, while hypocalcemia triggers secondary hyperparathyroidism, further promoting bone resorption and impairing skeletal strength (35, 36).

SSRIs have been shown to interfere with calcium homeostasis and bone turnover through several pathways. By inhibiting SERT, these drugs increase extracellular serotonin levels, especially in peripheral tissues. Elevated peripheral serotonin has been associated with reduced osteoblast differentiation and increased osteoclastic resorption, thereby worsening the imbalance in bone remodeling (29). When vitamin D and calcium levels are already insufficient, these drug-induced changes may lead to a compounded risk of osteopenia or osteoporosis.

Recent epidemiological studies have demonstrated a significantly higher prevalence of vitamin D deficiency among SSRI users compared to non-users. In a cross-sectional analysis involving older adults, vitamin D insufficiency was strongly associated with reduced BMD, particularly in femoral and vertebral sites (37). Moreover, low 25-hydroxyvitamin D [25(OH)D] levels in SSRI users correlated with increased parathyroid hormone (PTH) concentrations, suggesting compensatory mechanisms aimed at maintaining serum calcium at the expense of skeletal reserves (38).

The Endocrine Society's Clinical Practice Guidelines emphasize the importance of maintaining serum 25(OH)D levels above 30 ng/mL in individuals at risk for bone loss, including those on long-term SSRI therapy (39). Furthermore, the National Osteoporosis Foundation recommends calcium supplementation (1,200 mg/day) and vitamin D intake (800–1,000 IU/day) as essential for preserving bone health, especially in postmenopausal women and elderly men populations most commonly prescribed SSRIs (40).

Based on this evidence, it is clinically prudent to monitor serum vitamin D and calcium levels in individuals initiating or continuing SSRI therapy. Supplementation with vitamin D3 and calcium, dietary modifications, and regular physical activity are all critical components of a bone-protective strategy. Integrating these measures into the care of SSRI users can significantly reduce the risk of fracture and improve musculoskeletal outcomes.

5.4. Distinguishing Between Fall Risk and Direct Bone Effects

SSRIs increase the risk of bone fractures through two main mechanisms:

A) Indirect Effects via the Neurological and Musculoskeletal Systems

Common side effects of SSRIs include sedation, dizziness, ataxia, and psychomotor slowing. These effects can lead to balance disturbances and increased risk of falls, particularly in the elderly. One study indicated that the risk of falling is significantly elevated among SSRI users and may influence fracture incidence (41).

B) Direct Effects on Bone

SSRIs can directly affect bone metabolism through their impact on osteoblast and osteoclast cells. The presence of serotonin transporters and receptors in bone cells suggests that SSRIs can reduce BMD. Several studies have linked SSRI use to decreased BMD and an associated increase in fracture risk (42). A 10-year prospective cohort study in Canada demonstrated that SSRI/SNRI use was associated with an increased risk of fragility fractures, even after adjusting for other risk factors (43).

In the literature, there is debate regarding which mechanism bone quality deterioration or increased fall risk plays a more dominant role in the increased fracture risk associated with the use of SSRIs. Some researchers argue that the primary effect is on bone quality, while others emphasize the role of increased fall risk (44-46). The most accurate approach is to recognize that both mechanisms contribute and to closely monitor and manage both biological and functional risks during SSRI therapy.

6. Anatomical Dimension

Although SSRIs like sertraline affect the general structure of bone tissue, their impact appears to be more pronounced in certain anatomical regions. These are typically structures with high metabolic activity, load-bearing function, and susceptibility to morphological changes. The effects of sertraline on bone quality are more prominently observed in bones with high trabecular density.

6.1. Morphological Structure of Bones: Regions Susceptible to SSRI Effects

Anatomically, bones differ in structural density and functional roles, which results in regional variations in how SSRIs affect bone tissue (47). Due to their large surface area and rapid cellular turnover, regions rich in trabecular bone such as the vertebrae, femoral head, pelvis and mandible, may be more rapidly influenced by changes in osteoblastic and osteoclastic balance. In contrast, long bone diaphysis composed primarily of compact bone, such as the humerus and tibia, tend to be more resistant to these effects (48, 49). Considering serotonin's regulatory role in bone metabolism, it is plausible that SSRIs may exert anatomically distinct effects, though further comparative studies are needed to clarify site specific sensitivies.

6.2. Observed Changes in the Mandible, Femur, and Vertebra

The morphological responses of bone tissue to SSRIs vary depending on the anatomical site. In this context, the effects of sertraline use on high metabolic activity and clinically critical bones such as the mandible, femur, and vertebrae are particularly noteworthy (50).

The mandible, with its high trabecular bone content and dynamic remodeling capacity, is highly sensitive to SSRI effects. Recent studies show structural changes in the mandibular bone tissue of SSRI users, including reduced cortical thickness, decreased overall mandibular bone density, and marked alveolar bone resorption. These structural degradations are accompanied by increased tooth loss and widespread inflammation in periodontal tissues (51). Such mandibular changes may negatively affect dental implant procedures and extend healing times. Additionally, higher postoperative complication rates have been reported in SSRI users undergoing oral surgery (52).

The femur especially the femoral neck is one of the most frequent sites of osteoporotic fractures. SSRI use has been found to reduce BMD in this region by 5–10%, significantly increasing the risk of microfractures (53, 54). Cortical thinning and trabecular rarefaction also lead to decreased mechanical strength of the femur. Histological analyses in sertraline-treated animal models have revealed morphological abnormalities such as reduced osteoid volume, delayed mineralization, and irregularities on bone surfaces (55).

The vertebral column, due to its high trabecular bone content and constant load-bearing function, is another critical anatomical site susceptible to SSRI effects. Clinical and experimental studies indicate that SSRI use reduces the load-

bearing capacity of vertebral bodies and leads to trabecular thinning in the endplate regions (18, 34). Fat infiltration has also been observed in vertebral bone marrow, which is associated with suppressed bone formation. Vertebral compression fractures are more frequently observed in SSRI users, and high dose SSRI use has been correlated with reduced vertebral height, especially in postmenopausal women (37).

6.3. Evaluation in Terms of Musculoskeletal System Integrity

Structural weakening of bone tissue due to SSRI use negatively affects not only the skeletal system but also the overall integrity of the musculoskeletal system. SSRI-related osteopenia and osteoporosis can disrupt systemic integrity, compromising both biomechanical stability and functional capacity (38, 56). When BMD reduction is combined with age-related declines in muscle strength, fall risk significantly increases.

Furthermore, weakening at the muscle-bone interface increases tension at enthesis regions where tendons and ligaments attach to bone leading to complications such as microtears and soft tissue damage. Loss of joint stability in these areas may contribute to increased pain and restricted mobility, particularly in elderly individuals (57, 58).

In conclusion, SSRI induced bone weakening affects not only skeletal structure but also the functional capacity of the entire musculoskeletal system. This may result in increased difficulty performing daily activities, trauma from falls, and reduced quality of life.

6.4. Findings Supported by Histomorphometric Analyses

Histomorphometric analyses are extremely valuable for quantitatively evaluating the microscopic structure and cellular activity of bone tissue. SSRI use has been shown to cause significant changes in many of these parameters. Data obtained from animal models treated with sertraline provide strong evidence of impaired bone formation and increased resorption (59).

Following sertraline use, a significant reduction in the BV/TV ratio has been observed, indicating an overall decrease in bone mass. Similarly, reductions in Tb.Th and Tb.N have been reported. In contrast, Tb.Sp increases, meaning the trabecular structure becomes sparser and weaker (58, 60).

Examining the cellular populations on the bone surface, a notable decrease in the osteoblast surface (Ob.S/BS) has been observed, while the osteoclast surface (Oc.S/BS) has increased. This suggests a decline in bone formation accompanied by an increase in bone resorption. Additionally, the mineral apposition rate (MAR), which measures the rate of bone matrix mineralization, has decreased in SSRI-treated groups, indicating impaired bone renewal, and reduced mineral content (43, 61).

Altogether, these histomorphometric data demonstrate that sertraline causes significant cellular and structural deterioration in bone tissue, weakening the microarchitectural integrity and potentially increasing fracture risk.

7. Molecular Mechanisms

The effects of SSRIs on bone tissue are mediated not only systemically but also through cellular and molecular signaling pathways. SSRIs like sertraline have been shown to modulate the activity of bone-forming and bone-resorbing cells by targeting these molecular mechanisms (25). These processes operate through key biochemical pathways that regulate the balance between osteoblasts and osteoclasts.

7.1. RANKL/OPG System

The RANKL (Receptor Activator of Nuclear Factor κB Ligand) and OPG (Osteoprotegerin) system plays a critical role in the bone resorption process and is one of the primary regulators of osteoclastogenesis. RANKL, secreted by osteoblasts, binds to the RANK receptor on osteoclast precursor cells to initiate their differentiation and activation. OPG acts as a decoy receptor by binding RANKL and preventing the RANKL- RANKL interaction (62).

Recent experimental studies have shown that sertraline treatment can directly affect the RANKL/OPG ratio in osteoblastic and osteoclastic cell lines, disrupting bone homeostasis. This suggests that SSRIs can directly stimulate osteoclastic activity at the cellular level, providing a possible molecular basis for sertraline's bone resorption-enhancing effect (8, 61, 62).

7.2. Wnt/β-Catenin Signaling Pathway

The Wnt/β-catenin signaling pathway is one of the main regulators of bone formation, playing a key role in osteoblast differentiation and bone matrix synthesis. Wnt ligands bind to Frizzled receptors on the cell surface, promoting β-catenin accumulation in the cytoplasm and its translocation into the nucleus, where it activates target gene expression.

Some studies report that SSRIs inhibit this signaling pathway, suppressing β-catenin activity and thereby impairing osteoblast differentiation and bone formation (25, 63). The effect of sertraline on this pathway has been shown to be dose-dependent, with higher doses leading to more pronounced inhibition of Wnt signaling (64).

7.3. Serotonin Transporters and Bone Cells

The serotonin reuptake transporter (SERT) is expressed not only in the central nervous system but also in various peripheral cells, including osteoblasts and osteoclasts. Sertraline inhibits this transporter, increasing extracellular serotonin levels. However, serotonin has dual effects on bone tissue: while central serotonin promotes bone formation, peripheral serotonin may inhibit osteoblast activity.

Sertraline increases gut-derived peripheral serotonin, which may suppress osteoblast function. Moreover, changes in serotonin signaling caused by SERT inhibition have been reported to negatively affect intracellular calcium levels, mitochondrial function, and cell differentiation in bone tissue (13, 25).

7.4. Inflammatory Cytokines and Apoptosis

One of sertraline's potential effects on bone tissue is mediated through inflammatory responses and apoptosis mechanisms. Preclinical studies have shown that SSRI use increases oxidative stress in bone cells, elevating the expression of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α, which can trigger osteoblast apoptosis (23, 47, 65).

Cell culture experiments have demonstrated that sertraline administration in osteoblast-like cells leads to mitochondrial dysfunction, increased reactive oxygen species (ROS) production, and caspase activation (66). This process reduces the bone-forming capacity and disrupts the microarchitectural structure. To better illustrate these mechanisms, a schematic diagram summarizing the molecular-level effects of sertraline on bone metabolism is presented in Fig. 2.

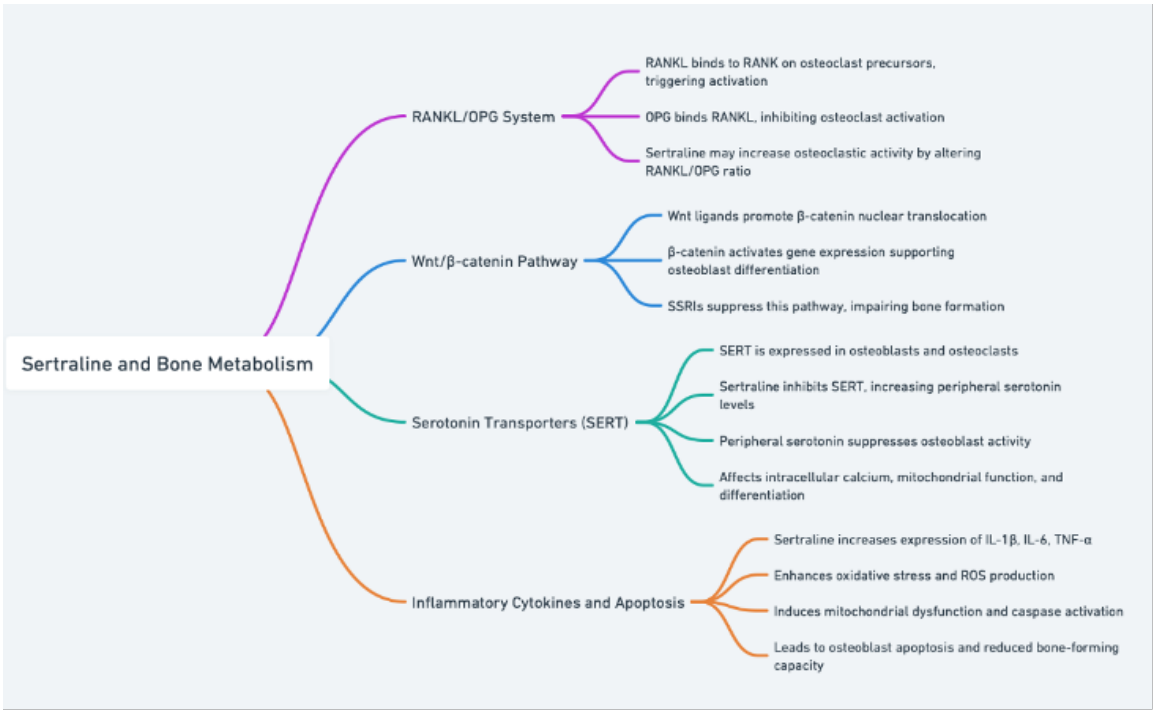

Fig. 2. Molecular pathways linking sertraline to bone metabolism

8. Sex, Age, And Genetic Factors

The effects of sertraline and other SSRIs on bone health vary significantly among individuals. These differences are thought to be influenced by several variables, including biological sex, age group, and individual genetic variations. Pharmacodynamic and pharmacokinetic responses to SSRIs can differ according to these factors, leading to varying profiles of drug-related bone resorption or mineral loss (24).

8.1. Sex Differences

Hormonal differences related to sex play a key role in bone metabolism. Estrogen levels, in particular, have a direct effect on osteoblast and osteoclast activity, making the balance between bone formation and resorption more delicately regulated in women. During the postmenopausal period, a decline in estrogen significantly reduces BMD, potentially exacerbating the adverse effects of SSRIs on bone (67).

Clinical studies show that bone loss and fracture risk associated with SSRI use are higher in women especially postmenopausal women than in men (33). On the other hand, some studies suggest that SSRIs may also indirectly affect testosterone levels in men, potentially impairing bone formation (5).

8.2. SSRI Use During Developmental Stages

Adolescence and young adulthood are critical periods during which bone mineral density increases rapidly and peak bone mass is achieved. The use of pharmacological agents that affect the serotonin system during this period may have a direct impact on bone development. In animal models, sertraline administration during developmental stages has been associated with reduced trabecular bone volume, delayed growth in the epiphyseal cartilage, and abnormalities in bone shaping (68).

Clinically, a significant association has been reported between long-term SSRI use in adolescents and lower BMD values. This may establish a foundation for an increased risk of developing osteoporosis later in life (69).

8.3. Genetic Susceptibility and Examples of Polymorphisms

Genetic variations in proteins involved in serotonin metabolism play a major role in individual sensitivity to SSRIs and, consequently, in their effects on bone. Polymorphisms in the SLC6A4 gene, which encodes the SERT, can affect drug transport and metabolism, thereby altering serotonin signaling in bone cells (69).

Moreover, certain variants in LRP5, a component of the Wnt signaling pathway, have been suggested to enhance SSRI-related bone loss. Mutations in the LRP5 gene are known to be associated with both high and low bone mass phenotypes, and the impact of SSRIs on this pathway may become more pronounced in the presence of a genetic predisposition (13).

Additionally, polymorphisms in the vitamin D receptor (VDR) gene have been reported to influence sensitivity in bone metabolism and may modulate SSRI-related bone mineral loss (70).

9. Discussion

The findings presented in this review indicate that sertraline and other SSRIs may exert significant effects on bone tissue, both morphologically and at the molecular level. Growing evidence suggests that the serotonin system influences not only neuropsychiatric processes but also bone metabolism, warranting a reassessment of SSRIs in the context of the skeletal system.

Animal models provide controlled experimental environments to investigate the direct effects of sertraline on bone metabolism. These preclinical studies are valuable for isolating the molecular and cellular consequences of pharmacological interventions. For instance, in rat and mouse models treated with sertraline, micro-CT and histomorphometric analyses revealed marked decreases in Tb.Th and bone volume BV/TV, along with significant increases in trabecular separation Tb.Sp and SMI values (12, 13).

Table 1. Comparison of animal and human data on the effects of SSRIs on bone

Criterion	Animal model data	Human clinical data
Model	Rat, mouse (preclinical experiment)	Retrospective/prospective cohort and case-control studies
Duration of Treatment	4–12 weeks	6 months to 10 years
Observed Changes	↓ BV/TV, ↓ Tb.Th, ↑ Tb.Sp, ↑ SMI	↓ BMD, ↑ fracture incidence
Measurement Method	Micro-CT, histomorphometry	DEXA (Dual-energy X-ray Absorptiometry), fracture records
Strengths	Mechanistic insight, molecular-level observation	Real-world data, translational relevance
Limitations	Not directly generalizable to humans, different metabolism	Confounding factors (depression, inactivity, nutrition)

In contrast, human clinical studies particularly retrospective cohort and case control designs have reported significant associations between SSRI duration/dosage and declines in BMD. Although these studies are based on population data, they are limited in their ability to establish direct causality due to confounding factors (4, 34, 56, 71). A detailed summary of the included animal and human studies, along with their methodologies and outcomes, is provided in Table 1.

Methodological differences between animal and human studies necessitate caution in interpreting the results. Therefore, the findings have been evaluated at two distinct levels of data and are comparatively presented in Table 2.

Table 2. Summary of included studies

Study	Model	Drug dose	Duration	Measurement method	Key Bone Outcomes	Effect Direction
Abu Nada et al., 2018 (22)	Rat	Sertraline (10 mg/kg)	4 weeks	Micro-CT	↓ BV/TV, ↓ Tb.Th	Negative
Howie et al., 2018 (14)	Mouse	Sertraline (5 mg/kg)	4 weeks	Histology	Minimal change	Neutral
Sheftel, 2022 (77)	Mouse (peripartal)	Sertraline (low dose)	3 weeks	DEXA	No change	Neutral
Diem et al., 2007 (4)	Human cohort	SSRI (varied)	>1 year	DEXA	↓ BMD	Negative
Rauma et al., 2016 (75)	Human cohort	SSRI	5 years	DEXA	↓ BMD, ~ fracture risk	Mixed
Wu et al., 2012 (74)	Meta-analysis	SSRI (varied)	Multiple studies	Varies	↑ Fracture risk	Negative

While animal models allow direct observation of pharmacological effects, human studies inherently involve numerous confounding factors. In mice administered sertraline, trabecular architecture has been shown to shift from plate-like to more fragile rod-like forms, resulting in reduced load-bearing capacity (12). Correspondingly, human studies have observed a correlation between SSRI use duration and reductions in BMD, along with increased fracture rates (34, 56).

However, the current literature is also marked by methodological limitations. In animal studies, differences in dosage, duration, and species and in human studies, retrospective design, confounding factors, and the inability to directly establish causality, all limit generalizability. Therefore, more prospective, randomized controlled trials are needed, along with personalized analyses assessing the

influence of pharmacogenetic variability.

Sex and age are key determinants in the relationship between pharmacological intervention in the serotonin system and bone metabolism. Postmenopausal women naturally undergo a decline in BMD due to estrogen deficiency. When combined with the suppressive effects of SSRIs on osteoblast activity, this physiological process can become pathological. Indeed, many studies have reported significantly increased risks of hip and vertebral fractures in postmenopausal women using SSRIs (34, 37, 56). In men, this effect appears less pronounced, although there is evidence that SSRIs may indirectly influence testosterone levels (55, 67). However, studies on male populations are limited in both number and sample size. Additionally, in individuals undergoing skeletal development (especially between ages 10 and 20), SSRI use has been associated with reduced bone mass accrual. Since this period is critical for peak bone mass acquisition, suppression of bone growth may lead to increased long-term risks of osteopenia and osteoporosis. For instance, a study reported significant decreases in lumbar BMD in adolescents undergoing long-term SSRI treatment (38).

All these findings indicate that SSRIs may have differing biological effects depending on age and sex, underscoring the importance of considering these variables in treatment planning.

At the molecular level, alterations in SERT, the RANKL/OPG pathway, and the Wnt/β-catenin signaling pathway play key roles in disrupting bone homeostasis. Polymorphisms in the SLC6A4 gene may influence serotonin transport and lead to individual variations in bone cell activity (2). Similarly, variants in the LRP5 gene may be determinants of SSRI-associated bone loss.

Evidence also shows that the effects of SSRIs are dose- and duration-dependent. Use for over one year has been correlated with significant reductions in BMD (72). However, the relatively minimal effects observed at lower doses highlight the need for careful investigation into the dose-toxicity relationship.

Although much of the literature on SSRIs and bone health points to adverse outcomes, some studies have reported minimal or statistically insignificant effects. For example, a large-scale cohort study found no direct association between SSRI use and fracture risk (27). Similarly, another study found no statistically significant difference in BMD values between SSRI-using adolescents and control groups (38). The discrepancy in results may stem from differences in study design (prospective vs. retrospective), follow-up duration, sample size, dosage, depression severity, physical activity, nutritional status, and vitamin D levels.

The majority of preclinical and clinical research indicates that SSRIs, such as sertraline, adversely affect bone microarchitecture by reducing Tb.Th, decreasing BV/TV, and increasing Tb.Sp (2, 9, 22). However, conflicting findings have been reported across the literature. In preclinical models, a study observed only mild reductions in trabecular bone parameters in sertraline-treated mice, without reaching statistical significance(14). Similarly, another study noted minimal changes in BMD among rats receiving low-dose sertraline, suggesting a possible dose-dependent effect (73). Clinical studies also demonstrate variability. Diem et al. reported BMD loss associated with SSRI use in older women, yet Wu et al., in a comprehensive meta-analysis of cohort and case-control studies, demonstrated that SSRI use was significantly associated with an increased risk of fractures, reinforcing the potential adverse skeletal effects of this class of antidepressants (4) (74). Rauma et al., in a 5-year longitudinal study from the OSTPRE cohort, demonstrated that although SSRI use accelerated bone mineral density loss, it did not significantly increase non-vertebral fracture risk. This divergence suggests that BMD reduction does not always translate into higher fracture incidence, potentially reflecting limitations in assessing bone quality solely by densitometry measures (75). Moreover, Williams et al. emphasized that SSRI induced skeletal effects may vary based on patient age, physical activity, and concomitant medical conditions (76). Choe et al. reported no significant deterioration in bone microarchitecture after long-term, low-dose sertraline administration in animal models, underscoring the role of baseline skeletal health and treatment parameters (77). Several factors may account for these discrepancies. Animal Model and Age Variability: Young animal models may exhibit skeletal plasticity that masks pharmacologic effects (2), whereas adult and aged models reveal more pronounced bone deterioration (22). Dosage and Treatment Duration: High-dose SSRI protocols are more consistently associated with adverse bone outcomes compared to low-dose regimens (9, 55). Measurement Techniques: Lower sensitivity of DEXA compared to high-resolution micro-CT may obscure subtle microarchitectural changes (4). Systemic Confounders: Factors such as baseline bone health, nutritional status, physical activity, and concurrent depression independently influence bone outcomes (78) (79). Indirect Effects via the Serotonergic Pathway: Yadav et al. proposed that serotonin signaling modulates osteoblast and osteoclast activity, suggesting complex regulatory mechanisms affecting bone metabolism (12). In summary, despite general evidence supporting a negative effect of sertraline on bone health, the heterogeneity among study designs, populations, and methodologies necessitates cautious interpretation. Future standardized, longitudinal, and mechanistic studies are needed to elucidate the true relationship between SSRI use and skeletal health. Moreover, some researchers propose that SSRIs may counteract the adverse effects of depression such as decreased physical activity and poor appetite thereby mitigating bone loss (2, 24). Therefore, a truly objective assessment of SSRIs' effects on bone health requires randomized controlled and prospective studies. Evaluations that isolate SSRI use from the

direct effects of depression may provide a clearer understanding of the drug's pharmacological impact.

In conclusion, although SSRIs are widely used in the treatment of psychiatric disorders, their effects on bone health are not sufficiently considered in clinical decision-making. It must be remembered that chronic SSRI treatment can produce systemic physiological effects beyond the neurological domain; thus, bone health should be addressed within a holistic therapeutic approach.

The studies reviewed in this article exhibit various methodological limitations. While animal models offer significant advantages for observing effects at the molecular level under controlled conditions, they are not directly generalizable to human physiology. Differences in species, metabolic rates, pharmacodynamics, and dose-response relationships introduce substantial variability. The age, sex, and dosage exposure in animal models often cannot be accurately translated to human equivalents.

Human studies, on the other hand, are mostly retrospective and prone to bias due to the lack of randomization and blinding. Furthermore, individuals taking SSRIs often present with confounding variables such as depression, physical inactivity, poor nutrition, comorbidities, and concurrent medication use. These factors make it difficult to isolate the effects of SSRIs on bone.

Additionally, the studies included in this review have assessed different bone regions (e.g., vertebra, femur, mandible), leading to site specific heterogeneity in the results. Measurement methods also vary while some animal studies use micro-CT and histomorphometry, human studies typically rely on macroscopic methods like DEXA (Dual-Energy X-ray Absorptiometry). These methodological inconsistencies reduce the comparability of outcomes.

Finally, many studies do not provide detailed information on clinical parameters such as duration of SSRI use, dosage, or concurrent medication. These omissions result in incomplete data for evaluating effect sizes.

Considering all these limitations, future prospective, randomized controlled studies should aim to improve methodological rigor and control for individual variables such as pharmacogenetics, age, and sex.

10. Future Directions

Although the current literature on the effects of SSRIs on bone health provides significant findings, it is still limited by methodological and content-related constraints. Studies that mechanistically explain the effects of SSRIs on osteoblast and osteoclast activity remain scarce and are predominantly based on animal models (12, 72, 80). Prospective and long-term follow-up studies based on human data are needed to more accurately assess the temporal progression and clinical outcomes of these interactions (81).

Future research should focus on the impact of various factors such as age (particularly adolescence and old age), sex differences, hormonal status (e.g., postmenopausal state), nutrition, and physical activity on the SSRI-bone metabolism relationship. Population-based cohort studies have the potential to analyze multidimensional relationships between SSRI use, BMD changes, fracture incidence, and biomarker levels.

Pharmacogenetic approaches are also gaining importance in this field. Polymorphisms in the serotonin transporter gene (SLC6A4) and bone regulation genes (such as LRP5 and VDR) may influence individual responses to SSRIs and their impact on bone metabolism, offering opportunities to personalize SSRI dosages.

Additionally, the use of advanced imaging techniques is crucial for evaluating micromorphological changes in bone tissue with higher sensitivity and quantitative accuracy. High-resolution peripheral quantitative computed tomography (HR-pQCT), micro-MRI, 3D histomorphometric analysis, and AI-assisted imaging software will enable both microscopic and longitudinal monitoring of SSRIs' effects on bone quality. Since the serotonin system functions not only within the central nervous system but also in many peripheral tissues, including the skeletal system, the development of holistic models that examine systemic as well as neuropsychiatric effects of SSRI treatment will pave the way for more effective scientific and clinical approaches in the future.

11.Conclusion

Sertraline and SSRIs in general should be carefully examined not only for their effects on the central nervous system but also for their impact on peripheral tissues particularly bone. The preclinical and clinical findings presented in this review demonstrate that SSRIs have multidimensional effects on bone metabolism. Specifically, suppression of osteoblastic activity, increased osteoclastic activity, and disruption of microarchitectural integrity can negatively influence bone quality.

The more pronounced morphological weakening observed in trabecular rich anatomical sites (e.g., vertebrae, femoral neck, and mandible) suggests that serotonin system sensitivity may vary regionally. On a molecular level, the RANKL/OPG balance, Wnt/β-catenin signaling pathways, and the distribution of serotonin transporters in bone cells provide critical insights into this pathophysiological process.

From a clinical perspective, bone health assessment is essential before initiating SSRI treatment in high-risk populations such as postmenopausal women, elderly individuals, and adolescents. Monitoring BMD during treatment, assessing vitamin D and calcium levels, and, if necessary, implementing osteoprotective therapies may help prevent skeletal complications associated with SSRI use.

In conclusion, the effects of sertraline on bone tissue should not be regarded merely as secondary side effects but rather as part of a systemic network of interactions that requires a multidisciplinary approach. Integrating knowledge from psychiatry, endocrinology, orthopedics, and molecular biology will facilitate the safe and personalized use of SSRIs. Monitoring the effects of SSRIs on bone health both at the fundamental scientific level and in clinical practice is essential for preserving the psychological and physiological well-being of the individual.

12. Limitation

Despite the comprehensive scope of this review, several limitations must be acknowledged. First, the majority of the included studies are preclinical animal models or retrospective clinical cohort studies, which inherently limit the generalizability of findings to broader human populations. High-quality randomized controlled trials (RCTs) investigating the skeletal effects of SSRIs, particularly sertraline, are scarce. Second, due to the considerable heterogeneity in study designs, populations, and outcome measures, a meta-analysis could not be performed. This restricts the ability to provide a quantitative synthesis of the overall effect size and introduces potential interpretation variability. Third, the measurement techniques employed across studies differ substantially. While some studies utilized highly sensitive imaging modalities such as micro-CT, others relied on DEXA, which may lack the resolution to detect subtle microarchitectural changes, possibly underestimating the true extent of skeletal deterioration. Fourth, the diversity of the study populations including variations in age, sex, menopausal status, baseline bone health, and comorbidities complicates direct comparison across findings and may contribute to the observed inconsistencies. Finally, the potential for publication bias cannot be excluded. Studies demonstrating significant adverse skeletal effects may be more likely to be published, while studies reporting no effect or protective outcomes may be underrepresented in the literature. Future research should prioritize prospective, large-scale, and standardized investigations, ideally incorporating both bone quality and clinical fracture outcomes to better clarify the skeletal consequences of long-term SSRI use.

Conflict of interest

The authors declared no conflict of interest.

Funding

No funding was used for the study.

Acknowledgments

None to declare.

Authors' contributions

Concept: B.N.Ö.E., Design: B.N.Ö.E., Data Collection or Processing: B.N.Ö.E., A.U., Analysis or Interpretation: B.N.Ö.E., A.U., Literature Search: B.N.Ö.E., A.U., Writing: B.N.Ö.E., A.U.

Ethical Statement

This study is a literature review and does not involve any human or animal subjects. Therefore, ethical committee approval is not required.

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