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REVIEW ARTICLE

Effects of Depression and Serotonergic Antidepressants on Bone: Mechanisms and Implications for the Treatment of Depression

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Abstract Osteoporosis is a chronic skeletal disease marked by microarchitectural deterioration of the bone matrix and depletion of bone mineral density (BMD), with a consequent increased risk for fragility fractures. It has been frequently associated with depression, which is also a chronic and debilitating disorder with high prevalence. Selective serotonin reuptake inhibitors (SSRIs), first-line agents in the pharmacological treatment of mood and anxiety disorders, have also been shown to negatively affect bone metabolism. SSRIs are the most prescribed antidepressants worldwide and a large number of persons at risk of developing osteoporosis, including older patients, will receive these antidepressants. Therefore, a proper musculoskeletal evaluation of individuals who are being targeted for or using SSRIs is a priority. The aim of this article is to review the evidence regarding the effects of depression and serotonergic antidepressants on bone and its implications for clinical care.

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Key Points

Depression is associated with bone deterioration and a consequent increase in fracture risk.

The use of selective serotonin reuptake inhibitors seems to independently worsen markers of bone health.

Both in vitro and in vivo evidence provides further support to the human clinical findings. However, the exact nature of the serotonergic pathways influencing bone and the direct and/or indirect effects are still unclear.

Given the evidence to date, risk assessments and recommendations for prevention and treatment of bone disease in psychiatric patients, particularly those of older age, should be considered.

1 Introduction

Osteoporosis is a chronic skeletal disease marked by microarchitectural deterioration of the bone matrix and depletion of bone mineral density (BMD), with a consequent increased risk for fragility fracture [1]. This increased propensity for fragility fractures is often associated with impaired mobility, resulting in decreased quality of life and significant social and financial burdens which further contribute to morbidity and mortality in this population [2, 3].

Osteoporosis is often associated with depression, also a chronic, debilitating, and highly prevalent disorder characterized by decreased mood, impaired cognitive functioning, and low energy levels, all of which impact overall quality of life [4]. Although there is some evidence that osteoporosis causes depression, probably due to the impaired quality of life caused by pain and fractures [5, 6], there is more detailed evidence supporting the hypothesis that depression negatively affects bone metabolism, particularly when the depressive disorder is treated with antidepressants [5, 7–11]. Selective serotonin reuptake inhibitors (SSRIs) are the most utilized group of antidepressants, constituting more than 60 % of all antidepressants prescribed worldwide [12]. SSRIs act by inhibiting the serotonin transporter to block serotonin reuptake and prolong extracellular activity [13]. Interestingly, serotonin receptors and the serotonin transporter have been reported in bone [14, 15], begging the question whether medications that antagonize serotonin reuptake could influence bone metabolism and consequently promote drug-induced osteoporotic fractures.

The aim of this article is to summarize the evidence identified through a search of the literature in PubMed prior to 2015 regarding the effects of depression and serotonergic antidepressants on bone and its implications for clinical care.

2 Depression, Bone Mass, and Fractures

There is a growing evidence base supporting the notion that depression may cause bone deterioration and consequently increase the risk of osteoporotic fractures in adults [5, 7–11]. Even when known risk factors for osteoporosis have been taken into consideration, bone mass has been shown to remain negatively associated with not only clinical depression but depressive symptoms [16, 17]. Furthermore, evidence suggests that this decrease in bone mass coincides with the onset of depressive symptoms, not just as a final consequence [18]. A systematic review and meta-analysis on the topic revealed that individuals with depression, compared with those without, display lower bone mass at the spine, hip, and forearm, with a stronger association observed for pre-menopausal than for post-menopausal women. This is likely due to the fact that post-menopausal women present other risk factors for osteoporosis, such as lower estrogen levels and physical inactivity, thus masking the association [9]. Similar conclusions were reached from a meta-analysis conducted by Wu et al. [19], which showed decreased bone mass at the spine and hip for both men and women with depression. Bone quality, as measured by qualitative ultrasound, has also been shown to be reduced among men and younger women with a history of mood disorders [20]. In summary, almost all studies support the existence of lower bone mass in persons with depressive disorder, and the presence of higher occurrence of fractures in this population. Notably, the increased rate of osteoporotic fractures associated with depression appears to be further exacerbated in antidepressant-treated compared with untreated individuals [21–25].

3 Use of Antidepressants and Risk of Fractures

The use of antidepressants, particularly those that block the reuptake of serotonin, has been linked with the development of osteoporosis and resultant fracture [11, 23–28]. A population-based, prospective cohort study performed in Canada measured the incidence of new fractures in more than 5000 adults 50 years or older over 5 years [29]. After adjusting for confounding variables, it was revealed that daily use of SSRIs independently doubled the risk of clinical fragility fracture. In addition, the effects were found to be dose dependent. Intermittent SSRI users also had an independent increased risk of incident clinical fragility fracture similar to that of daily SSRI users [29]. In another prospective, population-based cohort study of more than 7000 subjects over the age of 55 years [30], the risk of non-pathological, vertebral fractures in current SSRIs users was more than double that observed in past users of either SSRIs or tricyclic antidepressants. This study addressed the important issue of confounding by indication and demonstrated that SSRIs were a risk factor for fracture, independent of depressive symptoms. In addition, an analysis according to duration of SSRI use was performed (i.e., current SSRI use of fewer than 6 weeks, 6 weeks to 6 months, and longer than 6 months). These analyses revealed that all groups had an increased risk of non-vertebral fracture in comparison with non-users, with those who had been using SSRIs for less than 6 weeks being at greatest risk. A possible explanation for the increased risk of non-vertebral fracture seen with short-term SSRI use could be associated with the short-term adverse effects of SSRIs, such as bradycardia and orthostatic hypotension, which are likely to increase the risk of falls [30]. Depression has also been shown to be independently associated with an increased risk of falls [31]. In another population-based study [32], a time-dependent change in risk of hip fracture was observed. The increase in hip fracture incidence was higher in the first 14 days after initiation of SSRI treatment, and then tapered off after 42 days since first use. Again, the researchers hypothesized two different mechanisms of action: an initial increase in falls risk, probably due to adverse effects on postural stability, and a prolonged long-term effect due to medication-induced bone loss.

The Study of Osteoporotic Fractures also suggested that depression alone as well as SSRIs are associated with bone loss at the hip, even after adjusting for other risk factors such as physical activity and age [33]. This was an unexpected finding and highlighted that targeting depression with SSRIs actually potentiated the original risk. A further meta-analysis demonstrated that the use of SSRIs doubled the risk of fractures, with a dose-responsive association between SSRIs and fracture that directly correlated with the affinity for the serotonin transporter of each particular SSRI in the class [5, 24]. In addition, when compared with non-SSRI agents, SSRI agents increased the relative risk of fractures by more than 70 % [24]. These data are supportive of an argument that SSRI use may negatively impact bone metabolism, culminating in osteoporotic fracture.

4 Serotonin and Bone Metabolism

Bone is a multicellular organ, composed fundamentally of three major cell types: osteoblasts, osteoclasts, and osteocytes. Bone mass is maintained by constant bone remodeling that consists of bone resorption by osteoclasts and subsequent bone generation by osteoblasts. Osteocytes derive from osteoblasts that have become inserted in the bone matrix and remain interconnected to each other via long cytoplasmic processes, enabling them to act as mechano-sensory cells that coordinate the remodeling process in response to physical stressors [34].

It has been proposed that peripheral and central serotonin signaling have divergent actions on bone [35, 36]. Peripherally, serotonin directly activates osteoblastic serotonin receptors to inhibit bone formation, whereas centrally it inhibits the sympathetic nervous system, thus alleviating the negative adrenergic tone on osteoblasts. In the situation of elevated serotonin levels that result from treatment with SSRIs, the negative skeletal effects of peripheral serotonin may outweigh the positive skeletal benefits resulting from the enhanced central serotonin antidepressant and antisympathetic activity [37]. In addition to being produced in the brain, serotonin is also produced peripherally in the body, mostly by the gastrointestinal tract, as well as in the bone microenvironment itself by osteoclasts [38]. It is within this bone microenvironment that osteoclast-derived serotonin may act in a paracrine and autocrine manner to regulate other osteoclasts and also osteoblasts [39].

The precise mechanism by which peripheral serotonin influences bone metabolism has been a topic of controversy. Yadav et al. [35] first proposed that circulating serotonin reduced osteoblast proliferation directly via binding to the serotonin 5-HT_{1B} receptor (5-HT_{1B}R) on osteoblasts, and that circulating serotonin levels were controlled by the gene *LRP5* in the gut, which regulated expression of TPH1, the enzyme responsible for serotonin synthesis. A subsequent study by Cui et al. [40] challenged the notion of the role of serotonin in signaling to bone by showing that *LRP5* was directly implicated in osteocyte function; bone mass was decreased when *LRP5* was knocked out in osteocytes but not when knocked out in the gut. On the other hand, overexpression of *LRP5* increased bone mass when the overexpression was targeted to the osteocyte, but not when targeted to the gut.

The demonstration of serotonin receptors and/or a functional serotonin transporter in bone cells points to a direct action of serotonin in bone homeostasis. In osteoblast and osteoblast cell lines, it is mainly 5-HT_{1A}R, 5-HT_{2A}R, and 5-HT_{2B}R protein expression and/or binding sites that have been observed [41, 42]. Of these, only expression of the 5-HT_{2B}R is increased during osteoblast differentiation [43]. Mice deficient of the 5-HT_{2B}R have been shown to have accelerated age-related low turnover bone loss, secondary to impaired osteoblast function [43]. Conversely, mice deficient in osteoblastic 5-HT_{1B}R display a phenotype characterized by high bone mass, secondary to an increase in the number of osteoblasts and, consequently, bone formation [35].

Disruption of the serotonin transporter gene or pharmacologic inhibition of the transporter by SSRIs produces a low bone mass phenotype in growing mice. For example, mice carrying the null mutation of the serotonin transporter gene displayed reduced bone mass, altered trabecular architecture, and inferior bone mechanical properties compared with controls, while bone mass has been shown to be impaired in both growing and adult mice treated with SSRIs [44–46].

More recently, an increase in bone mass has been observed in growing mice in which TPH1 was knocked out globally, which resolved at maturity [38]. This increase in bone mass in growing mice was subsequently shown to result from a defect in osteoclast resorption. Normal osteoclasts were shown to be capable of synthesizing serotonin, whereas osteoclast differentiation was impeded in precursor cells deficient in TPH1 [38]. This result showed that osteoclasts are a source of serotonin in the bone microenvironment. Osteoclastogenesis appears to be controlled by a paracrine/autocrine mechanism involving serotonin, which may also be sufficient to induce osteoblast proliferation. TPH2 has also been shown to be implicated [36, 47]. Taken together, these data generated in animal models proposing a direct role for serotonin in bone homeostasis allow the referential framework that posits that SSRIs may possess direct anti-anabolic skeletal effects, through the pharmacological inhibition of the serotonin transporter.

5 Final Recommendations

There is a growing body of evidence substantiating the notion that antidepressants, particularly those in the SSRI class, might decrease bone mass, and as a consequence magnify the risk of osteoporosis and osteoporosis-related fractures. This is particularly relevant since the major indication of SSRIs is depression, a condition also associated with low bone mass, osteoporosis, and non-pathological fractures. Both depression and osteoporosis are highly prevalent. While osteoporosis is generally more prevalent in the elderly, the path to osteoporosis begins in childhood with a variable process of bone accrual, and evolves throughout adulthood with a similarly variable process of bone loss. Considering that SSRIs are the most prescribed antidepressants worldwide, a large number of persons at risk of developing osteoporosis will receive antidepressants, which means individuals with an already increased risk of fractures are exposed to an even greater risk. It also needs to be stressed that many of the risks for depression overlap with those for osteoporosis, such as physical inactivity, poor diet, and smoking. This makes a proper musculoskeletal evaluation of individuals who are being targeted for SSRIs a priority, and serial evaluations with bone scans and initiation of anti-osteoporotic medications should be considered in subjects with an already increased baseline risk for osteoporosis (such as the elderly).

Compliance with Ethical Standards

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Conflict of interest Brisa S. Fernandes, Jason M. Hodge, Julie A. Pasco, Michael Berk, and Lana J. Williams have no conflicts of interest regarding this subject.

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