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Review article

Serotonin reuptake inhibitors and bone health: A review of clinical studies and plausible mechanisms

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ABSTRACT

Selective serotonin reuptake inhibitors (SSRIs) are currently the treatment of choice in depression and constitute major portion of prescription in depressive patients. The role of serotonin receptors in bone is emerging, raising certain questions regarding the effect of blockade of serotonin reuptake in the bone metabolism. Clinical studies have reported an association of SSRI antidepressants which with increase in fracture and decrease in bone mineral density. This review focus on recent evidence that evaluate the association of SSRIs with the risk of fracture and bone mineral density and also the probable mechanisms that might be involved in such effects.

1. Introduction

Osteoporosis is the disease characterized by low bone mass, deterioration of the bone tissue and enhanced bone resorption that is not compensated by enhanced bone formation and consequently leading to increase fracture risk [1]. Due to its prevalence worldwide, osteoporosis is considered a serious public health concern. It was estimated that over 200 million people worldwide suffer from this disease, the worldwide annual incidence of hip fracture was approximately found to be 1.7 million [2]. Secondary osteoporosis is characterized by number of factors such as medical conditions (Cushing syndrome, rheumatoid arthritis, and serious kidney failure), hormonal causes (hyperparathyroidism, diabetes) or certain medications. One of the major factors governing the progression of secondary osteoporosis is long-term usage of corticosteroid, anticancer, anticonvulsant, antipsychotic and antidepressant drugs.

Depression is a major public health problem and a leading cause of disability and according to the study from National Health and Nutrition Examination Survey, half of the patients with moderate to severe depression undergo treatment with antidepressants [3]. Majority of the patients undergoing antidepressant medications rely on two classes of drugs, tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs), however, the 2 classes of antidepressants appears to have the same efficacy for the treatment of depression [4], yet SSRIs were found to be more preferred due to better patients compatibility due to less anticholinergic adverse effects [5]. The study regarding the evaluation of the prescribing pattern has shown increased prescribing of SSRIs (63%) as compared to serotonin nor-epinephrine reuptake inhibitors (SNRIs) (14%) and other antidepressants in Europe [6], however the same studies also reported variation between the countries, for example, prescribing patterns for SSRIs varied from 32% in Germany to 82% in France, and SNRIs from 6% in Austria to 26% in the Netherlands.

With the chronic usage of certain class of antidepressant medication, the risk of secondary cause of osteoporosis has increased. The patient does not get aware of his situation until fracture happens which is further diagnosed to be associated with osteoporosis. Since many years, there have been discussions about the possibility for SSRIs to enhance the risk of bone fractures. Various proposed causes such as the medical conditions and

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treatments have shown to enhance the incidence of falls, especially in the elderly [7]. Studies have reported bone loss and reduced bone mineral density (BMD) by these antidepressant medications [8,9]. The present review focuses on the available clinical evidence on the association of SSRIs with fracture risk and BMD. In addition, a mechanistic basis by which these SSRIs may have effect on bone is discussed.

2. SSRIs and risk of fractures

The association between the antidepressants and the risk of fracture has been the subject of various observational studies, generally case-control and cohort. The result of these studies indicates that SSRIs increase the risk of fractures as compared to the nonusers (Table 1). The initial study was carried out by Liu studying 8239 cases with hip fracture and showed the increase in the risk of hip fracture with the use of SSRIs [10]. The largest study to date is a case-control analysis in Danish national registers, which compared 124,655 cases with fracture and 373,962 controls and found the increased risk of hip and vertebral fractures with the users of SSRIs as compared to the nonusers [11,12]. This study also defined the differences among the classes of antidepressants. While the use of fluoxetine, citalopram and sertraline was associated with increase in the risk of fracture, dose dependently but the same was not found with paroxetine. However, not all studies agree to this, for instance, a cohort study on 10,844 patients failed to detect any risk of fracture by the use of SSRIs [13].

A study in the Netherlands demonstrated an early increase in the risk of fracture which reached peak within 8 months of SSRI use but the same was found to be reduced after the discontinuation of the medication [14]. A much recent meta-analysis carried out by Rabenda et al. [8], involving 34 studies (20 case-control studies and 14 cohort studies) showed that 26 studies reported an association with nonvertebral fractures, 19 on hip fractures and 3 studies on spine fracture with the use of SSRIs and concluded that use of antidepressants is associated with an increase in the risk of fractures as compared to the nonusers. However, they also concluded that the SSRIs are more risk prone for the fractures as compared to the TCAs. The study carried out by Moura et al. [15] potentially demonstrated the role of SSRIs and SNRIs on bone in a population based Canadian multicentre osteoporosis study involving 9423 patients and showed increased risk of fragility fracture by the use of SNRIs as compared to the nonusers. Another very recent case-control study in Taiwanese population showed that the risk of fracture is increased by 2.7 times in old patients those who are currently using SSRI [16]. The studies evaluating the association of SSRIs with fracture risk is tabulated (Table 1). While SSRI's could be held responsible for the increase in fracture as per Table 1, it is pertinent to review the influence of SSRIs on BMD since fractures could also be related to the impact caused to the bone by falling/accident. Overall, the studies have potential confounders but the association of fracture with the SSRIs usage is seen, we need more prospective studies to minimize the confounders and strengthen the facts.

3. SSRIs and BMD

There have been a number of cross-sectional and cohort studies regarding the use of antidepressants and reduced BMD (Table 2). A cross-sectional study in 5995 men reported a significant reduction in hip BMD (4%) and spine BMD (6%) with the SSRI use as compared to the nonusers [17] which was further confirmed in a cohort study including nearly 3000 women divided into 3 categories SSRI users (198), TCA users (118), and nonusers (2,406). After 5 years, the bone loss was highest among SSRI users (0.8% reduction in BMD) but unchanged in TCA users. The results were adjusted for confounders and surprisingly there was no difference in the result for continuous and intermittent SSRI users [18]. Various studies on relatively small population showed similar results [19,20]. A recent cross-sectional study by Rauma et al. [9] including 928 men (47 SSRI, 9 SNRI, and 9 TCA users) demonstrated reduced BMD in the SSRIs and SNRIs users. However, there is not much evidence to validate the SNRI use and reduced BMD. Overall, the data suggests that the current use of the SSRIs is associated with the bone loss and reduction in BMD. However, further research is required to define the effect on BMD on SNRIs use. The data is summarized in Table 2 and this decrease in BMD following SSRIs usage leads to increase in fracture risk [21] as shown in Table 1. BMD measurements can be used as a predictor of the fracture risk as any small but significant difference increases the relative risk of fractures [22].

4. SSRIs and bone turnover markers

Studies evaluating the effect of SSRIs on bone turnover markers are limited. A randomized placebo controlled trial carried out in United States evaluated the effect of escitalopram on bone turnover markers and concluded that the drug does not alter the same in short-term usage [23]. The author also confirmed that the results of the said study could not be generalized for other SSRIs usage for long term (Table 3).

5. Confounders in the clinical studies

Unlike the animal studies the research in human has lots of the confounding factor that need to be addressed [24]. As depression itself is one of the major factor that cause loss of bone mass in nearly all the age group in different population but it was seen that both depression and SSRI's independently acts on bone by different mechanism to cause it loss thus bone loss is accelerated in depressive patients taking SSRI's [25–27]. Other confounders are smoking, alcohol consumption, age, gender, dairy product consumption, sun exposure, food supplements, disease condition, low body mass index, ethnicity, comorbidities, concomitant medication and we do not have enough studies to discuss the issues for these confounders [26,28,29].

6. Probable mechanistic evidence for SSRIs induced alterations in bone

SSRIs are more concentrated in the bone marrow as compared to the brain or blood [30]. Thus, there is an increased concern that SSRIs have a significant impact on the bone metabolism. Since SSRIs enhance the presynaptic availability of serotonin (5HT) by inhibiting the serotonin transporter (5HTT) resulting in blocked reuptake of 5HT from extracellular space [31], it is important to understand the role of serotonin in bone.

Serotonin is basically a monoamine that is produced within the neurons located in the raphe nuclei [32] and sends impulses to the different regions of the brain by being released into the synaptic cleft and binding to the post synaptic receptors. 95% of serotonin is synthesized in the periphery in the gut (heterochromaffin cells) thus regulates gastrointestinal functions [33], also in endothelial cells in the lungs [34] and in the platelet granules [35]. The major enzymes involved in the synthesis of the serotonin is tyrosine hydroxylase (TPH), which exist in two isoforms TPH1 in the gut and TPH2 in the brain. As serotonin cannot cross the heteroencephalic barrier, it forms 2 functionally separate pools i.e., within central nervous system and peripheral system. The role of serotonin on the bone was first documented in 2001 when researchers showed the presence of serotonin receptors, neurotransmitters and