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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

Table 1
Effect of SSRIs on fracture risk in various clinical studies.

Author	Study type	Population	No. of users	SSRI users vs. nonusers (adjusted odd ratio 95% CL)	Conclusion
Liu et al., 1998 [10]	Case-control study (Canada)	8239 Cases with hip fracture 41,195 controls	540 SSRI users	Hip fracture: 2.4	SSRI use is associated with increased risk of hip fracture.
van Staa et al., 2002 [41]	Case-control study	16,449 patients (men and women)	–	Fracture: 1.5	SSRI are associated with risk of fracture.
Hubbard et al., 2003 [42]	Case-control study (UK)	16,341 Cases with hip fracture 29,889 control	1901 SSRI users	In first 14 days, hip fracture: 4.76 hip fracture: 1.8	Increased risk after 14 days of treatment with SSRIs however SSRI further increase the risk.
Ensrud et al., 2003 [43]	Population-based cohort study	8127 Women 4.8-yr follow-up	501 Antidepressant users	Hip fracture: 1.54	SSRI are associated with risk of hip fracture.
French et al., 2005 [44]	Case-control study (USA)	2212 Cases with hip fracture 2212 controls	–	Doubled risk of hip fracture	SSRI use is associated with increased risk of hip fracture.
Lewis et al., 2007 [45]	Prospective study in men	5995 Men, 4.1-yr follow-up	–	Nonvertebral: 1.65	Use of SSRI was found to effect nonvertebral fractures.
Vestergaard et al., 2008 [12]	Case-control study (Denmark)	124,665 Cases with fractures 373,962 control	–	Any fracture: 1.4, hip fracture: 2.02	A dose-response relationship for SSRIs was observed.
Spangler et al., 2008 [46]	Prospective cohort study (USA)	82,410 Women, 7.4-yr follow-up	–	Hip fracture: 1.33	SSRI use increased the risk of hip fracture.
Ziere et al., 2008 [47]	Prospective population-based cohort study	1219 Patients with nonvertebral fracture	–	Nonvertebral: 2.35	SSRI use increased the risk of nonvertebral fractures.
Abrahamsen and Brixen, 2009 [48]	Case-control study (Denmark)	15,716 Men with fracture, sex matched controls	–	Hip fracture 2.0	SSRI use increased the risk of hip fracture.
van den Brand et al., 2009 [14]	Case-control study (The Netherlands)	6763 Cases with hip fracture 26,341 controls		Hip fracture: 2.35	Rapid increase in the risk of fractures.
Verdel et al., 2010 [49]	Case-control study (The Netherlands)	16,717 Cases with fracture, 61,517 controls	–	Osteoporotic fracture: 1.95	SSRI use increased the risk of fracture.
Diem et al., 2011 [50]	Cohort study (USA)	8217 Women. 6-yr follow-up	91 SSRI users	Hip fracture: 1.01	No increase in the risk factor by SSRI use.
Gagne et al., 2011 [13]	Medicare data (USA)	5422 Patients	2711 SSRI users	Hip fracture: 1.33	SSRI but not TCA use increased the risk of fracture
Wu et al., 2012 [51]	Meta-analysis	13 Observational studies	–	Fracture: 1.40	SSRI use increased the risk of any fracture.
Eom et al., 2012 [52]	Meta-analysis	12 Observational studies	–	Fracture: 1.69	SSRI use is associated with increased risk of fracture.
Bakken et al., 2013 [53]	Cohort study on older people (Norway)	904,422 People, 39,938 people with hip fracture	–	Hip fracture: 1.8	SSRI use increased the risk of hip fracture.
Rabenda et al., 2013 [8]	Meta-analysis	34 Studies (1,217,464 individuals)		Nonvertebral fracture: 1.65, hip fracture: 1.64	SSRI show a higher increase in risk of fracture as compared to TCA.
Moura et al., 2014 [15]	Population-based Canadian multicentre osteoporosis study	9423 Patients	6645 SSRI/SNRI users	Fragility fracture: 1.8	Use of SSRI/SNRI increased the fragility rate.
Sheu et al., 2015 [54]	Prospective cohort study	40- to 64-yr female patients	137,031 SSRI user vs. 236,294	Increased fracture risk: 1.76	Use of SSRI appear to increase fracture risk among middle-aged women
Wang et al., 2016 [55]	A population-based nested case-control study	8250 Patients and 33,000 matched control	4729 SSRI users, 659 SNRI users, 3259 nonusers	Increased fracture risk: 1.16 with SSRI/SNRI use	Use of SSRI/SNRI is associated with increased risk of fracture.
Hung et al., 2017 [16]	Case-control study	4891 Cases vs. 4891 control	–	Increased fracture risk by 2.17-fold increase in the odds of hip fracture in the elderly by SSRI use.	Current use of SSRI increases the risk of fracture in old people.

SSRI, selective serotonin reuptake inhibitor; CL, confidence limit.

transporters in the bone cells (osteoblast and osteoclast) [34,35].

Gut and brain serotonin was found to have different actions on the bone metabolism by acting through different pathways. Gut derived serotonin reduces the osteoblast proliferation and thus leads to bone loss and brain derived serotonin decreases sympathetic output and thus favors bone formation [36]. The opposite effects of gut and brain serotonin on the osteoblasts is depicted in Fig. 1. Gut derived serotonin, the free circulating serotonin which signals the osteoblast by binding to the receptor Htr1b expressed on the surface of osteoblast, inhibits the phosphorylation of cAMP-responsive element binding protein (CREB) by phosphokinase A (PKA), leading to the reduced expression of cyclin genes and thus decreased osteoblast proliferation [36]. Similarly Oury et al. [37], also shows that gut derived serotonin acts on Htr1b receptor in osteoblast which in-turn decrease phosphorylation of CREB by PKA leading to reduced osteoblast proliferation and bone loss. A very major role in this pathway is mediated by Wnt β-catenin signaling. Wnt is basically a cystine rich secreted glycoprotein whose genes was discovered in mouse mammary) tumor (int-1) and Drosophila melanogaster (wingless) and both encodes for same proto oncogene and so dubbed as Wnt [38]. Wnt proteins inhibit LDL-receptor related protein 5 (LRP5), thus inhibits TPH1 and gut serotonin

Table 2
Effect of SSRIs on bone mineral density in various clinical studies.

Author	Study type	Population	SSRI users vs. nonusers (adjusted odd ratio 95% CL)	Conclusion
Kinjo et al., 2005 [56]	Cross-sectional analysis in the NHANES	14,646 Adults, 154 patients on antidepressants	No association	No association between SSRI use and BMD
Cauley et al., 2005 [57]	Cross-sectional analysis (USA)	5995 Old men (65 yr of age)	Femoral BMD decreased by 3.5% and lumbar BMD decreased by 3.7% in users	SSRI use is associated with decreased BMD
Diem et al., 2007 [18]	Cohort study (USA)	2722 Women, 5 year follow-up	Hip BMD decreased by 0.8% in users vs. 0.5% in nonusers	SSRI use is associated with decreased BMD
Haney et al., 2007 [17]	Cross-sectional analysis (USA)	5995 Men	Hip BMD 4% lower in users	BMD is lower in patients taking SSRI
Richards et al., 2007 [58]	Population-based cohort (Canada)	5008 Adults, 5-yr follow-up	Hip BMD reduced by 4% in users	BMD reduced in the SSRI uses
Mezuk et al., 2008 [59]	Case cohort study	98 vs. 398, 23-yr follow-up	Association in women not in men	Antidepressant medication use was associated with decreased BMD in women but not in men.
Spangler et al., 2008 [46]	Prospective cohort study	6441 Women, 3-yr follow-up	No association	SSRI use not associated with a change in BMD
Williams et al., 2008 [19]	Cross-sectional analysis (Australia)	124 Women	Reductions in femoral neck BMD (6%), trabecular BMD (6%), and forearm BMD (4%) in users	SSRI use lowers BMD at certain sites.
Calarge et al., 2010 [20]	Cross-sectional analysis (USA)	45 Out of 83 on risperidone and SSRI, adolescents	SSRI use associated with lower trabecular BMD	SSRI use reduces BMD in adolescents.
Cauley et al., 2010 [60]	Cross sectional study (USA)	3670 Men	Femoral BMD decreased by 0.86% in users Lumbar BMD decreased by 6.6% in users	SSRI use is associated with decreased femoral and lumbar BMD.
Diem et al., 2013 [61]	Prospective cohort study	311 User vs. 1590 nonuser	BMD decreased on average 0.68% per year in nonusers, 0.63% per year in SSRI users	Use of SSRIs and TCAs was not associated with an increased rate of bone loss at the spine, total hip or femoral neck.
Gebara et al., 2014 [27]	Nineteen observational studies	Adults aged 60 and older	Two longitudinal studies showed association between SSRI/SNRI and reduced BMD	Decreased BMD was associated with use of selective reuptake inhibitors
Ak et al., 2015 [62]	Observational cross-sectional study	60 Postmenopausal women with generalized anxiety disorder, 12-mo SSRI therapy	Reduced lumbar and femoral BMD as compared to 40 nonusers	SSRI use is associated with the reduced BMD in postmenopausal women
Rauma et al., 2015 [9]	Cross-sectional study	928 Men, 47 SSRI users, 9 SNRI users	Decreased BMD with SSRI/SNRI use	SSRI/SNRI use was associated with lower BMD only in lower-weight men (<75–110 kg)
Feuer et al., 2015 [29]	Cross-sectional analysis of data from NHANES study	4303 Patients (12–20 yr), 62 of 4303 on SSRIs	3.2% lower BMD in SSRI users as compared to nonusers.	Need for future studies to examine effects of SSRI use on bone mass in adolescents.
Rauma et al., 2016 [63]	Longitudinal study	1669 Nonusers vs. 319 SSRI's user	Decrease in BMD was observed for SSRI user.	SSRI shows the accelerated bone loss.

SSRI, selective serotonin reuptake inhibitor; CL, confidence limit; NHANES, National Health and Nutrition Examination Survey; BMD, bone mineral density.

Table 3
Effect of SSRIs on bone biomarker in clinical studies.

Author	Study type	Population	SSRI users vs. nonusers	Conclusion
Diem et al., 2014 [23]	Randomized controlled trial	40–62 yr, in good health, and in the menopause transition or postmenopausal.	62 Escitalopram vs. 72 placebo	There was no effect on serum CTX and P1NP level after 8 wk of the treatment with Escitalopram.

SSRI, selective serotonin reuptake inhibitor; CTX, carboxy-terminal cross-linked telopeptide of type 1 collagen; P1NP, procollagen type 1 amino-terminal propeptide.

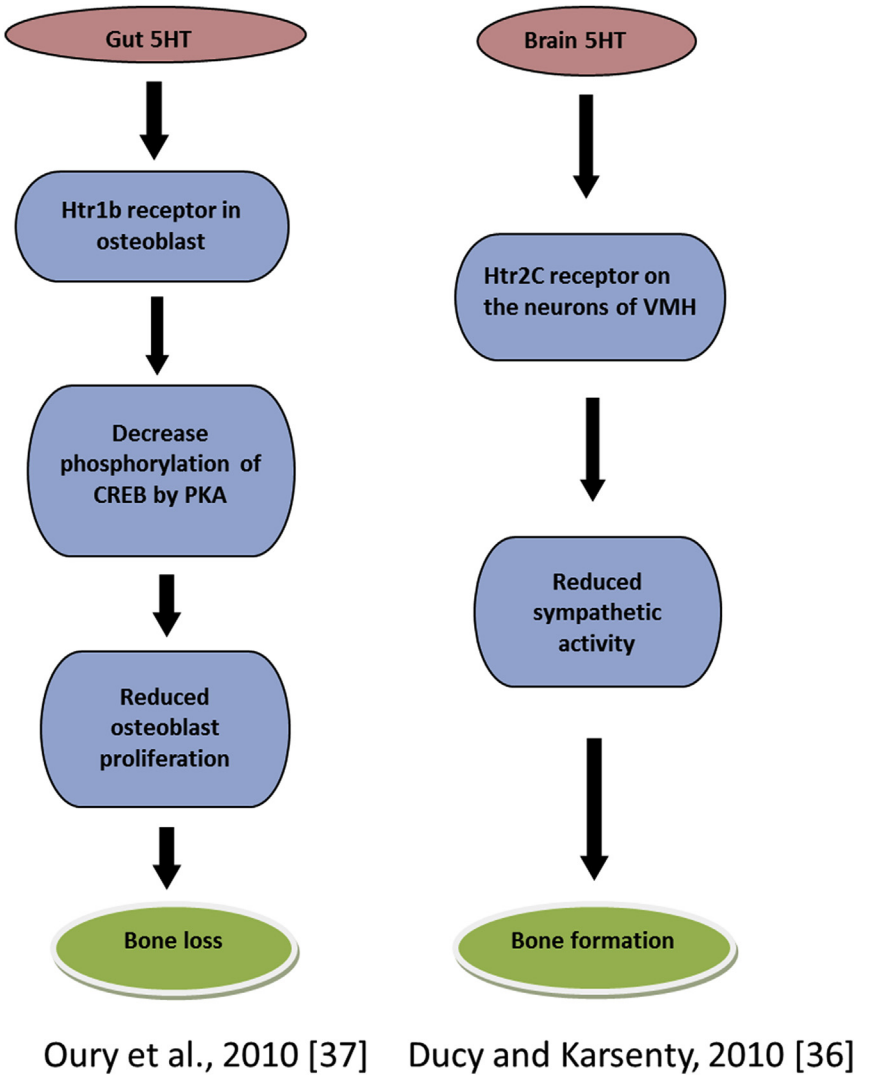

Fig. 1. The flowchart describes the opposite effects of the brain and gut derived serotonin on the osteoblast by acting via 2 different receptors. Htr1b present on the osteoblast binds to the gut derived serotonin and promotes bone loss, however the Htr2c receptor present in the brain binds to the brain derived serotonin and promotes bone formation via signaling through β2 adrenergic receptors present on the osteoblast. 5HT, serotonin; VMH, ventro-medial hypothalamus.

synthesis. Wnt β-catenin signaling has demonstrated a major role in controlling osteoblast differentiation, proliferation, survival and bone formation. Binding of Wnt to the frizzled receptor induces destabilsation of destruction complex, leading to the accumulation of unphosphorylated β-catenin which translocates to nuclues to form complex with members of T cells specific transcription factor of DNA binding proteins to regulate transcription of osteoblast target genes and osteoprotegrin [39]. Thus, the gut derived serotonin in association with the Wnt signaling functionally modulate the osteoblast proliferation. In a remarkable work by Yadav et al. [40], it was shown that LRP5 dependent mechanism is responsible for bone structuring as it hinders the TPH1 expression and serotonin amalgamation in enterochromaffin cells leading its tying on Htr1b serotonin and inhibiting CREB outflow to decrease in cyclin D1 expression and osteoblast proliferation. Brain derived serotonin, on the other hand, signals to the ventromedial hypothalamic neurons via Htr2c receptors, which reduces the epinepherine/sympathetic tone and this reduced sympathetic outflow is relayed to the β2 adrenergic receptors on the osteoblast which enhances the bone formation and reduces bone resorption via molecular clock/cyclin D and PKA/activating transcription factor 4 dependent pathway [36]. The differential effects of the gut and brain derived serotonin on bone pathophysiology is represented in Fig. 2. Recently, a new mechanism is suggested by Ortuno et al. [24], that the SSRIs may act independently on osteoclast's Ca++ calmodulin-dependent activation of c-Fos–Nfatc1 cascade leading to decrease in bone resorption. While it also acts on brain-derived serotonin's reuptake which in-turn results in desensitizing of Htr2c leading to increase in sympathetic tone which in-turn enhances the bone resorption and decreases the bone accrual. For the shorter duration of use of SSRI, the independent effect on the bone i.e., decrease in bone resorption predominate while on long-term use, both independent and serotonin-mediated effect counteract each other leading to bone loss.

7. Conclusions and future prospects

The understanding of the molecular basis of the serotonin on bone and the differential effects of the gut and brain derived serotonin on the bone highlights number of areas for subsequent

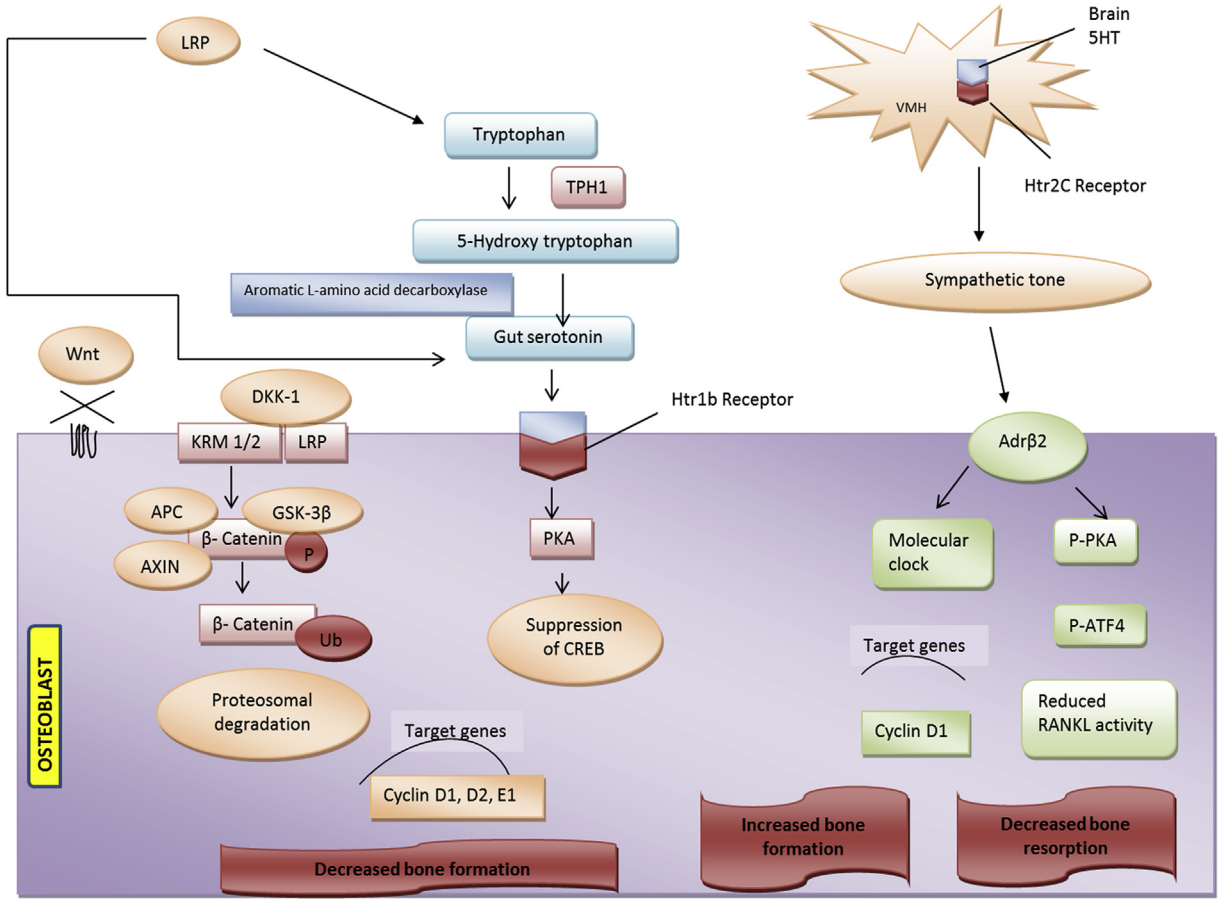

Fig. 2. The figure describes the different effects of gut and brain serotonin on the osteoblast. The free circulating gut-derived serotonin directly signals the osteoblast by binding to the Htr1b receptor. The binding inhibits the phosphorylation of CREB by PKA, leading to the reduced expression of cyclin genes and thus decreased osteoblast proliferation. Wnt signaling plays a crucial role in the process, binding of Wnt to the frizzled receptor induces destabilsation of destruction complex, leading to the accumulation of unphosphorylated β-catenin which translocates to nucleus to form complex with members of T cells specific transcription factor of DNA binding proteins to regulate transcription of osteoblast target genes and osteoprotegrin. In contrast, serotonergic neurons signals to VMH neurons via Ht2C receptor inhibit synthesis of epinephrine and thus decrease symathetic tone. This decrease is relayed in osteoblasts by decreased signaling via β2 adrenergic receptor, which negatively controls osteoblast proliferation via a molecular clock gene/cyclin D1 and positively regulates bone resorption via activation of a PKA/ATF4-dependent pathway, leading to increased synthesis of receptor activator of nuclear factor kappa-B ligand. The inhibition of sympathetic activity by brain-derived serotonin thus results in increased formation and decreased resorption. 5HT, serotonin; LRP, low-density lipoprotein receptor-related protein' TPH, tyrosine hydroxylase 1; VMH, ventro-medial hypothalamus; CREB, cAMP-responsive element binding protein; Adrβ2, adrenergic β2 receptor; APC, adenomatous polyposis coli; GSK, glycogen synthase kinase; PKA, phosphokinase A; ATF4, activating transcription factor 4.

research in this direction particularly in animal models for exploration of plausible mechanisms. Available literature suggests that there is still need for more investigation into the effect of SSRIs on bone when clinically used. However, the role of the concomitant medications, co morbidities and other confounders involved (for example, depression itself is a potential confounder) is an important shortcoming in clinical studies. There remains a stringent need for the further clinical research into the dose-response relationship and the effects during the chronic treatment across different SSRI's. There is need for more prospective studies from the depressed patients and the meta-analysis of the adverse event data from randomized control trials of the antidepressant medications, also the monitoring of bone health should be done in the interest of the patients who are on the chronic treatment of SSRI for better and safe treatment.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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