# Selective serotonin reuptake inhibitors and bone health

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Studies demonstrating lower bone mineral density among depressed patients have led to the investigation of antidepressant medications and bone health. It remains unclear whether the depressed state itself or antidepressant treatment is responsible for these findings. Several recent observations support a role for serotonin in bone health. Serotonin transporters have been documented in osteocytes, osteoblasts and osteoclasts. Mice with disruption of the serotonin transporter gene have an osteopenic phenotype. Cohort studies in humans have demonstrated lower bone mineral density, higher rates of bone loss and fracture among those using selective serotonin-reuptake inhibitors compared with those on other antidepressants (primarily tricyclic antidepressants) and those on no antidepressant medication. Areas of future research may include clarifying the role of depression and antidepressant therapy (and the interaction between the two) on bone health, determining potential sources for serotonin in bone cells, identifying mechanisms to explain the impact of serotonin on bone and understanding how serotonin-transporter genetics impact bone.

**Keywords:** antidepressant medications, bone mineral density, depression, fractures, osteoporosis, selective serotonin uptake inhibitors, serotonin, serotonin transporter

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Depression has been associated with low bone mineral density (BMD) in some but not all studies. Several mechanisms have been proposed to explain the association. Recently, antidepressant medications have been implicated as a factor impacting bone health and a potential explanation for increased rates of hip fracture and lower BMD among depressed patients. The potential effects of psychotropic agents on skeletal health is part of a broader evolving interest in the effects of the nervous system on bone. Although various neurohormonal signaling mechanisms are present in bone, the serotoninergic system has a clear clinical correlation: selective serotonin reuptake inhibitors (SSRIs) are a commonly used class of antidepressants that function by blocking the serotonin transporter.

A role for serotonin as a link between depression and bone loss is supported by several recent observations. First, functional serotonin transporters have been documented in bone. Second, mice with disruption of the serotonin transporter gene have lower bone mass, size, strength and formation rates than wild-type mice. Third, the use of antidepressant medications that block the serotonin transporter increases the risk of osteoporosis and fractures. Further research is needed to understand the source of serotonin acting on bone cells and to define the exact mechanisms by which depression and antidepressants effect bone health. If current findings are substantiated, patients taking antidepressants (particularly SSRIs) could be targeted for screening and preventive care to detect and manage osteoporosis. This article will review the effects of neurohormonal modulation on bone, specifically with regard to the effects of depression and antidepressant therapy.

## Evidence for neural regulation of bone metabolism

The process of bone remodeling is dynamic and responsive. Hormonal, paracrine/autocrine and mechanical signals enable osteoblasts and osteoclasts to adapt and respond to physiologic stress [1]. Bone tissue is richly innervated by sympathetic and sensory neurons. Several neurotransmitters and neuroactive peptides have been shown to have significant effects on bone. Studies of an energy-regulating peptide, leptin, provide important evidence for the skeletal effects of the nervous system. While leptin has osteogenic effects when introduced systemically [2,3], when administered directly into the cerebroventricular space of the brain it has antiosteogenic effects [1,4,5]. These antiosteogenic effects are mediated through hypothalamic neural circuits [5,6], with signals being relayed downstream to osteoblasts and osteoclasts via the sympathetic nervous system [1,4]. In addition, neuropeptide Y and hypothalamic Y2 receptors, which are involved in appetite control, regulate bone formation via a central mechanism that appears to use signaling pathways distinct from leptin [6].

Neuropeptides also have local effects on the skeleton. The nerve terminals innervating bone contain several neuropeptides: vasoactive-intestinal peptide, pituitary adenylate cyclase-activating

peptides, neuropeptide Y, substance P and calcitonin gene-related peptide, to name a few [7–13]. Bone cells contain receptors for these peptides and activation of these receptors alters bone-cell activity [10,12,14,15]. Likewise, alterations in bone metabolism influence how densely the bone is innervated [16]. These findings provide evidence for a functional link between the nervous system and bone.

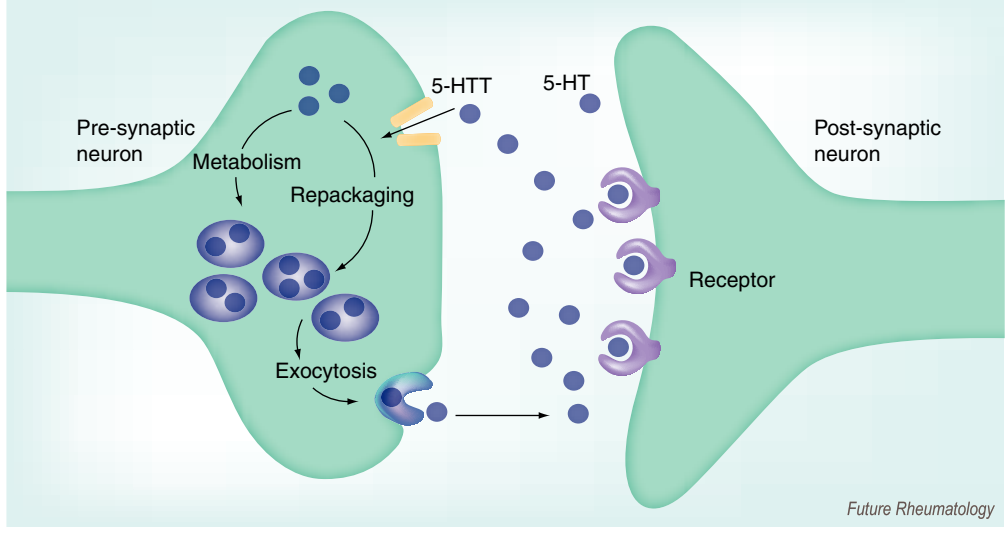
Further evidence documenting a functional link between the nervous system and bone has been provided by studies of neurotransmitters and their transporters. Various neurotransmitters and transporters have been associated with alterations in bone metabolism. For example, osteoblasts possess functional receptors for the neurotransmitter glutamate [17], and the glutamate/aspartate transporter in osteocytes is influenced by osteogenic mechanical stimuli [18]. Meanwhile, mice with altered dopamine transporter function have a skeletal phenotype of reduced cancellous bone mass, cortical thickness and mechanical strength [19].

## Functional serotonin pathways in bone

Recently, attention has focused on serotonin (5-HT) signaling within bone. Serotonin is a monoamine neurotransmitter, with defined roles in the CNS, gastrointestinal tract and cardiovascular system. In the CNS, it is produced by presynaptic neurons and released into the synaptic cleft to activate pre- and post-synaptic serotonin receptors to influence a range of behavioral, physiological and cognitive functions (**Figure 1**) [20,21]. In the gastrointestinal tract, serotonin is produced and secreted by enterochromaffin cells in response to mucosal stimulation, before diffusing to enteric nerve endings to stimulate peristalsis [22,23]. In both the CNS and gastrointestinal tract, the duration and intensity of serotonergic activity is regulated by the serotonin transporter (5-HTT), a sodium-chloride-dependent transporter, which reuptakes released serotonin to control synaptic and extracellular concentrations (**Figure 1**) [24,25]. In the cardiovascular system, serotonin is primarily taken up by platelets via a 5-HTT and stored in dense granules [26]. It is released following platelet activation to cause either blood vessel constriction or dilation [27], and smooth muscle cell hypertrophy and hyperplasia [28].

In the skeleton, functional receptors for serotonin have been identified in primary and clonal osteoblasts, osteocytes and periosteal fibroblasts, a population containing osteoblast precursor cells [29–31]. Serotonin receptor agonists in avian periosteal fibroblasts induce proliferation [31]. A serotonin analogue modulates the response of osteoblasts to mechanical stimulation [31]. Serotonin also increases whole-cell cyclic AMP and prostaglandin $E_2$ levels in a murine osteocytic cell line [29].

**Figure 1. Serotonin and serotonin transporter in the nervous system.**




Selective 5-HT-reuptake inhibitors inhibit 5-HTT, thereby increasing synaptic serotonin concentrations. 5-HTT promoter polymorphisms affect the number of transporters expressed by the presynaptic neuron. 5-HT: Serotonin; 5-HTT: Serotonin transporter.

In addition to serotonin receptors, osteoblasts, osteoclasts and osteocytes all possess the 5-HTT [29,31,32]. Binding and uptake studies demonstrated the 5-HTT in osteoblastic and osteocytic cells to be functional and highly specific for serotonin uptake [29,30]. Inhibition of the 5-HTT by fluoxetine in osteoclast cells inhibited differentiation but not activation in one study [32]. However, fluoxetine affected the total number of differentiated osteoclasts and bone resorption in a bell-shaped manner in a separate study [33]. Thus, the entire serotonin signaling pathway (receptors and transporter) is present in bone. These functional serotonergic pathways for both responding to and regulating the uptake of serotonin, suggest that serotonin and the 5-HTT may be involved in bone metabolism [18,30]. Based on this knowledge, one can postulate that alterations in bone serotonin levels have the potential to cause downstream events that regulate bone mass, geometry and strength. Since serotonin and the 5-HTT play important roles in major depressive disorder and other affective disorders [34,35], interest has focused on the relationship between serotonin-related disease states, such as depression, treatment options that effect the serotonin transporter, bone health (BMD or fractures) and bone metabolism.

## Evidence for serotonin impact on bone

### *Genetic mouse models of 5-HTT transporter disruption*

Mice with 5-HTT gene disruption have lower bone density, size, strength and formation rates. Using two differing animal models, Warden and colleagues found altered serotonin signaling to have significant detrimental effects on bone mineral accrual in growing mice [36]. Mice with a lifelong null mutation of the gene encoding for the 5-HTT (knock-out mice) display a consistent skeletal phenotype of reduced mass, altered architecture and inferior mechanical properties. These mice have lower whole body bone mineral content (BMC) and lower BMC at the spine, femur and cranium. Histomorphometric analysis of distal femur trabecular bone shows that knock-out mice have lower trabecular bone volume, fewer trabeculae and greater spacing between trabeculae than their wild-type counterparts. Using microcomputed tomography to measure cross-sectional geometry at the midshaft femur demonstrates that knock-out mice have smaller bones than wild-type mice. This decrease in area results from reduced bone size; cortical thickness is equivalent between the two groups. Exposing femurs and tibias to mechanical stress (three-point bending) leads to earlier breaking (lower force needed) in the knock-out mice. Additionally, knock-out mice have lower endocortical and periosteal bone formation than wild-type mice [36].

The exact mechanism whereby the 5-HTTs and serotonin receptors regulate bone mass is unknown. Reduced bone formation is present in both weight-bearing (femoral) and nonweight-bearing (cranial) bones, indicating that behavioral alterations in the knock-out mice, leading to reduced physical activity, do not account for the decreased bone formation [36]. The primary defect in the 5-HTT-null mice, therefore, appears to be a defect in osteoblastic bone formation.

### *Pharmacologic mouse models of serotonin disruption*

Wild-type mice treated with the SSRI fluoxetine demonstrate decreased rates of bone formation at both cortical and trabecular sites, and decreased whole body BMC [36]. In growing mice, this leads to reduced bone mineral accrual. Similar to the genetic mouse model with disruption of the 5-HTT, the skeletal phenotype results from a reduction in bone formation, indicating an osteoblastic phenotype.

By contrast, Battaglino and colleagues treated a different mouse strain (Swiss-Webster vs Black Six) with fluoxetine for 6 weeks and found that trabecular bone formation increased at both the femur and the vertebrae. Ovariectomized mice treated with fluoxetine experienced bone loss at the same rate as those not treated [32].

## Clinical experience with SSRI therapy: developmental effects on bone

Serotonin signaling has been shown to be important in embryonic development, specifically neural crest migration and differentiation [37,38]. While SSRIs cross the placenta and are secreted in breast milk, their use during or after pregnancy does not appear to alter development [39–41] or influence skeletal morphology [42–48]. SSRI use may have more subtle effects on bone health, however. A number of studies have demonstrated that infants of mothers taking SSRIs during pregnancy and lactation have reduced birth weight and weight gain [42,45,49]. Although this has been disputed by other studies [43,50,51], any SSRI effects on weight early in life may be relevant to the skeleton, as birth weight and weight gain in infancy are determinants of bone mass later in life [52–54].

## Clinical experience with SSRI exposure: epidemiologic studies

Evidence for the effects of neurotransmitters on bone in humans derives mainly from studies of depression, antidepressant treatment and BMD or fractures. Depression tends to increase with age, just as the risk for osteoporosis and hip fracture is increasing. Treatments for depression often involve modulation of the serotonin signaling system through blockage of the serotonin transporter. SSRIs are potent and specific inhibitors of the 5-HTT, and are considered first-line therapy for depression because of their safety, efficacy and ease of administration [55]. Other antidepressive therapies may also block the 5-HTT, but with much lower potency and specificity.

Depression has been associated with lower BMD in some [56–63], but not all, studies [64–67]. Certain studies used select psychiatric populations, which may have influenced the results [56,59,61,63]. Depression may also contribute to risk of hip fracture; whether this relationship is mediated by falls is not yet clear.

Antidepressants have also been demonstrated to affect bone outcomes. Table 1 summarizes epidemiologic studies containing 500 or more participants that evaluate associations between antidepressants and skeletal outcomes. A complicating factor in the evaluation of the effect of depression and SSRIs on bone health is confounding by indication [68]. Since both depression and its treatment (with SSRIs or other antidepressant medication) have the potential to influence skeletal health, studies of either, that do not control/adjust adequately for the other, could give misleading results. Many of the studies performed to date have failed to adequately assess for either depression or antidepressive treatment.

Recent studies have used large data sets to evaluate antidepressant medications and bone, attempting in various ways to adjust for depression. One study used the Medicare Current Beneficiary Survey to examine and reanalyze results from other published studies that found associations between SSRI use and hip fracture. After adjusting for residual confounding variables not found in the administrative data sets used for original analyses (body mass index, smoking, activities of daily living score, cognitive and physical impairment), SSRI use continued to be associated with a significant risk of hip fracture [69].

In a cross-sectional analysis of data from 5995 men aged 65 years and over participating in the osteoporotic fractures in men (MrOS) study, adjusted mean BMD among SSRI users was 3.9% lower at the total hip and 5.9% lower at the lumbar spine as compared with men reporting no antidepressant medication use ($p \leq 0.001$ for all). Mean BMD was not significantly lower for men using trazodone or tricyclic antidepressants. Adjustments for depressed mood using components of the short-form 12 did not significantly alter these results. The observed size effect of SSRIs was similar to the well-known detrimental effect of corticosteroids on bone loss [70].

Among 2722 elderly women, SSRI use was associated with significantly higher rates of bone loss at the hip and assessed longitudinally over an average of 4.9 years, controlling for possible confounders, including depressive symptoms (measured using the Geriatric Depression Scale [GDS]) [71]. Those using SSRIs had an average decrease in total hip BMD of 0.82% per year compared with 0.47% per year for nonusers ($p < 0.001$). Those using tricyclic antidepressants had an average decrease of 0.47% per year ($p = 0.99$) compared with nonusers. SSRI users also had higher rates of bone loss at the femoral neck and trochanter. Excluding women who scored at least 6 on the GDS did not significantly change the results.

Finally, a study of 5008 men and women aged 50 years and over found SSRI use to be associated with lower BMD, falls and increased clinical fragility fracture after adjusting for depressive symptoms, other medication use, falls and other potential covariates. Importantly, these data included information on the dose of medication and the effects were dose-dependent. Depressive symptoms alone were not associated with fractures. The relationship between SSRIs and fracture could be at least partially explained by an increased risk of falls and a potentially clinically relevant decrease in BMD among SSRI users [72]. Further research is needed to confirm and expand upon available studies.

## Conclusion

Presence of serotonin receptors and transporters in bone suggests a potential role for serotonin in bone metabolism. Several studies in mice support the hypotheses that disruption of the serotonin system, either genetically or pharmacologically, negatively impacts bone health. In humans, evidence is mounting for an effect of SSRIs on bone density and fracture. Definitive conclusions remain problematic because of the potential effects of serotonin on skeletal health, and the issues of confounding by indication.

**Table 1. Antidepressant use associations with bone mineral density and fracture.**

| Study | Study design, n, population | n (%) on medication | BMD | Fracture | Comments | Ref. |
|---|---|---|---|---|---|---|
| Liu (1998) | Administrative database: case-control method, using data from 8239 cases of hip fracture > age 60 years, hospitalized between April 1994 and March 1995 for hip fracture from the Canadian Institute for Health Information (with data available to link with Ontario Drug Benefit programme) and 41,195 controls from the Registered Persons Database (Ontario Ministry of Health) | SSRIs: 6.6% of cases and 2.8% of controls; TCAs: 11.6% of cases and 7.7% of controls | Not evaluated | SSRIs and TCAs associated with increased risk of hip fracture | OR for hip fracture for SSRIs > secondary-amine TCAs > tertiary-amine TCAs. OR for new vs continuous users was signficant for secondary and tertiary amine TCAs but not for SSRIs | [86] |
| Ensrud (2003) | Prospective cohort of 8127 women age ≥ 65 years (SOF) | SSRIs: 103 (1.3%); TCAs: 353 (4.3%) | Not evaluated | Risk for hip fracture appeared to be increased for all antidepressant users (SSRI and TCA). The association between medication use and hip fracture was signficant only for women taking TCAs | | [87] |
| Hubbard (2003) | Administrative database: case-series method, using a longitudinal data set 1987–1999: 16,341 patients and 16,341 matched controls (GPRD) | SSRIs: 955 (5.8%) of cases; 892 (3.0%) of cases; TCAs: 2908 (17.8%) of cases, 2544 (11.9%) of controls. | Not evaluated | SSRIs and TCAs associated with higher rates of fracture | Effects seen within the first 14 days of treatment | [85] |
| Kinjo (2005) | Cross-sectional analysis of 14,646 adults from NHANES III data (1988–1994) | Antidepressants 154 (1.1%) | SSRIs not associated TCAs not associated | Not evaluated | Data shown for combined (SSRI and TCA) antidepressant users. Authors state that reduced BMD was not detected among either TCA or SSRI users | [64] |
| Richards (2007) | Prospective cohort of 5008 men and women > age 50 years (CaMOS). | SSRIs: 137 (2.7%) TCAs: 162 (3.2%); Depressive symptoms: 609 (12.2%) | SSRIs associated with lower BMD. TCAs not evaluated | SSRIs associated with higher rate of fracture. TCAs not evaluated | Dose-dependent increase in fracture for SSRIs. SSRIs associated with higher risk of falls | [72] |
| Haney (2007) (In press) | Prospective cohort of 5708 men ≥ age 65 years (MrOS) | SSRIs: 137 (2.6%); TCAs: 99 (1.7%); Trazodone: 52 (1.1%) | SSRIs associated with lower BMD. TCAs not associated with BMD | Not evaluated | | [70] |
| Diem (2007) (In press) | Prospective cohort of 9704 women ≥ age 65 years | SSRIs: 198 (0.7%) TCAs: 118 (0.5%) | SSRIs associated with higher rate of bone loss. Rate of bone loss for TCA users equivalent to antidepressant nonusers. | Not evaluated | | [71] |

*BMD: Bone mineral density; CaMOS: Canadian Multicentre Osteoporosis Study; GPRD: General Practice Research Database; MrOS: Osteoporotic Fractures in Men; NHANES III: National Health and Nutrition Examination Survey III; SOF: Study of Osteoporotic Fractures; SSRI: Selective serotonin reuptake inhibitor; TCA: Tricyclic antidepressant .*

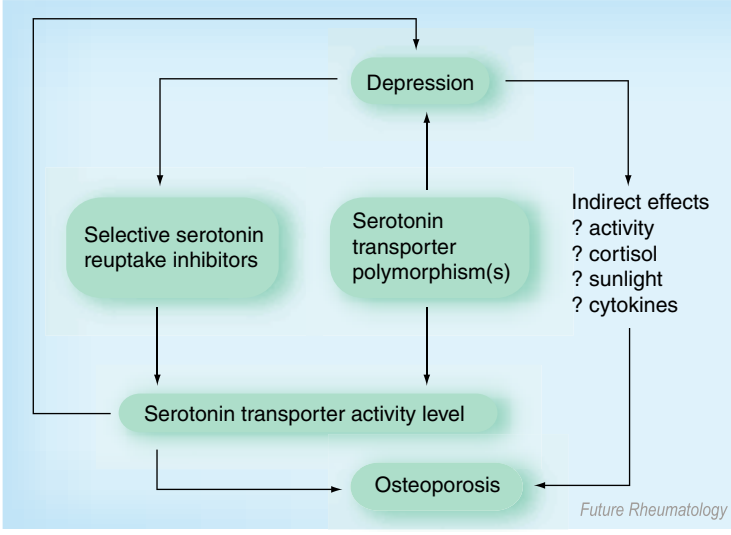
## Future perspective

### *Sources of serotonin*

Serotonin receptors and transporters are expressed in bone but, thus far, studies have failed to convincingly demonstrate a source of serotonin in bone. This raises an important question. For serotonin pathways to be clinically relevant in the skeleton, serotonin must be available as a ligand for bone cells. While this issue has not been rigorously investigated, skeletal serotonin has the potential to be derived from indirect or direct sources. Indirect sources for serotonin synthesis and release are nonskeletal (e.g., the gut or platelets) and require subsequent transport to skeletal sites. Platelets store serotonin in dense granules and release it only following activation [26], so the serotonin derived from the gut and circulating in the platelets is unlikely to represent a useful source of serotonin for bone cells. Similarly, serotonergic neurons have not been identified in bone. The blood–brain barrier is impermeable to serotonin, making it also unlikely that serotonin within the CNS can influence bone cells located in the periphery.

As external sources appear unlikely sources of serotonin for bone, it is possible that bone cells produce serotonin. Recent evidence suggests that both osteoblasts and osteocytes are potentially capable of synthesizing serotonin, since they express the rate-limiting enzyme for serotonin synthesis (tryptophan hydroxylase) [29]. Confirmation of intracellular synthesis of serotonin would indicate that serotonin effects within the skeleton may be autocrine/paracrine in nature.

**Figure 2. Potential mechanisms for a relationship between depression and osteoporosis.**




### *Serotonin transporter genetics*

Genetic variations within the 5-HTT and receptor genes have the potential to impact the system of neuroendocrine signaling within bone, but this has not been thoroughly explored. The 5-HTT is encoded by a single gene (*SLC6A4* ) located on chromosome 17q11.1–q12. Two common polymorphisms in the *5-HTT* gene have been widely studied: the promoter region of this gene has either a 44 bp insertion (L allele) or deletion (S allele) [73]. A variable number tandem repeat (VNTR) region has been identified in intron 2 with either nine, ten or 12 repeats of a 16–17 bp unit [74].

Studies on the 5-HTT have demonstrated correlations between the short allele and a number of mental states related to serotonin: affective disorders including depression [74–79], suicidal behavior [73], seasonal affective disorder [75] and anxiety-related personality traits [81,82]. Likewise, studies examining the VNTR polymorphism in intron 2 of the 5-HTT have found a higher prevalence of the 9-repeat allele in patients with affective disorders [76,77]. Preliminary data suggest that the two polymorphisms may be associated with bone mass. In a study of 500 elderly men, the 9-repeat allele of the 5-HTT was associated with a 12% higher BMD at the trochanter (adjusted means: 0.759 vs 0.880; $p = 0.019$) and a 10% higher BMD at the total hip (adjusted means: 1.050 vs 0.955; $p = 0.08$) after adjusting for age and lean body mass. The L-allele was associated with a 4% lower BMD at the femoral neck (0.777 vs 0.811; $p = 0.032$) [78].

Thus far, gene association studies of the 5-HTT have primarily used a candidate gene approach, investigating the two alleles described above in association with mental health disorders [79]. Difficulties associated with this method, including population admixture (nonrandom mating) [80] and haplotype block conservation [81], may explain inconsistent results [82,83]. There has been little exploration of the variation that exists within the rest of the gene and full characterization of the extent of variation in the 5-HTT and association with bone mass and fracture risk is necessary [84].

### *Confounding by indication*

The mechanisms whereby depression may influence skeletal health are complex and interrelated. The model in **Figure 2** illustrates potential mechanisms for a relationship between depression and osteoporosis, specifically a direct effect on bone mediated by the 5-HTT. Effects on

bone among depressed patients may be due to medications (SSRIs in particular), via their effect on 5-HTT activity. The 5-HTT itself might impact transporter activity and/or depressive symptoms and severity. Finally, depression may lead to decreased physical activity, high cortisol levels and low exposure to sunlight; these factors and others have the potential to contribute to differences in bone health seen in this population. To settle this question, prospective, randomized studies that use rigorous measures of depression and control for potential confounders (such as cortisol levels) are needed.

## Screening

Finally, the most critical question is whether people with depression and/or antidepressant use warrant increased surveillance for bone loss. If evidence supporting a role for either depression or antidepressant treatments in bone loss and fractures continues to accumulate, clinicians will be faced with questions about appropriate strategies for screening of osteoporosis in patients with depression or taking antidepressants. Future research should address whether screening could impact outcomes in these populations, as well as what types of therapies are appropriate for treating low bone mass in depressed patients.

## Acknowledgement

*This publication was made possible by grants from the National Institute of Arthritis and Musculoskeletal and Skin Diseases: AR 051926 (Haney) and AR 052018 (Bliziotes). We thank Lynn Kitagawa for her assistance with the figures.*

## Executive summary

### *Neural regulation of bone metabolism*

- Bone is innervated by sympathetic and sensory neurons.
- Nerve cells terminating in bone contain several neuropeptides.
- Bone cells have receptors for neuropeptides and are negatively affected by the absence of neuropeptides.

### *Functional serotonin pathways in bone*

- Functional serotonin receptors are present in osteoblasts, osteoclasts, osteocytes and periostial fibroblasts.
- Functional serotonin transporters are present in osteoblasts, osteoclasts and osteocytes.

### *Evidence for serotonin impact on bone:* in vivo *data*

- Mice with disruption of the serotonin transporter gene have lower bone density, size, strength and bone formation rates and lower whole body bone mineral content.
- Mice treated with selective serotonin-reuptake inhibitors (SSRIs) show lower bone formation and lower whole bone mineral content.

### *Evidence for serotonin impact on bone: epidemiologic data*

- Depression has been associated with low bone density and hip fracture in some studies.
- SSRI treatment has been associated with low bone density and hip fracture in some studies.
- It remains unclear whether antidepressant medication or the disease state of depression itself is the cause of these findings.

### *Future perspective*

- Further research is needed into potential sources for serotonin in bone.
- Interactions between depression, antidepressant medications, bone density and fracture are complicated and may be multifactorial.
- Genetic polymorphisms at the serotonin transporter impact its activity and, therefore, have the potential to impact its effect on bone.
- Clinical questions about screening patients with depression and those receiving antidepressant therapy for bone loss have yet to be addressed.

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