Serotonin: A New Potential Risk Factor for Falls, Low BMD, and Fracture

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Serotonin is a neurotransmitter present in the central nervous system (CNS) and intestine. It binds to the 5-hydroxytryptamine (5-HT) receptor, and regulates gastrointestinal (GI) movements and CNS signaling resulting in changes in mood and memory, as well as cardiovascular effects, including vasoconstriction and blood flow. The 5-HT receptors are mainly G-protein coupled receptors that may mediate excitatory and inhibitory signaling. The 5-HT receptors come in a variety of forms in the different organs mediating various effects. Importantly, 5-HT receptors are also present in bone.\(^1\)

It has been proposed that peripheral and central 5-HT receptor modulation and serotonin levels may have different effects on bone.\(^2\) Tryptophan, which can be converted into serotonin in the CNS, may affect bone positively, and an opposite effect of peripheral gut and central CNS serotonin has thus been suggested.\(^3\) Several drugs, particularly selective serotonin reuptake inhibitors (SSRIs) alter serotonin signaling. The SSRIs have been associated with an increased risk of fractures.\(^2\) However, little is known about the effects on bone and fracture risk of other frequently used drugs interacting with the 5-HT receptors such as ondansetron, prucalopride, and ergotamine.\(^3\) An interaction between any underlying disease such as major depressive disorder, serum serotonin, and the risk of fractures is also possible. For example, ondansetron underlying cancer may confound the picture.

Changes in CNS signaling as well as changes in blood pressure and blood supply to the bones may affect fracture risk, by affecting bone density and bone formation. Changes in CNS processing, awareness, and central perfusion may increase the risk of falls through alterations in postural control. Both bone density and falls may thus be at play as risk factors for fractures linked to serotonin levels and receptor affinity and receptor sensitivity both peripherally and centrally.

High plasma serotonin has been linked to low bone mineral density (BMD),\(^4,5\) although this has not been reproduced in all studies.\(^6,7\) The associations have been modulated by weight and have been different in premenopausal and postmenopausal women and between men and women.\(^7\) Even positive associations with serum serotonin have been reported for whole-body and femur BMD. Although this potentially could indicate a relationship with sex steroid levels, no association with estradiol levels could be demonstrated.\(^7\)

Notably, in carcinoid syndrome with excess production of serotonin and its metabolites no changes in BMD have been observed.\(^8\) The lack of an association in the presence of very high serotonin levels—well beyond physiological levels—may indicate a change in receptor sensitivity to serotonin. Therefore, the relationship between circulating serotonin and BMD remains controversial.

Even fewer studies have assessed the relationship between serum serotonin and risk of fractures.\(^5,9\)

In the study published in the current issue of the *JBMR*, Kristjansdottir and colleagues\(^9\) addressed this question using the Swedish MrOS cohort; and reported an increased risk of hip fractures and nonvertebral fractures with increasing serum serotonin levels, whereas no association with vertebral fractures was found. The association between serum serotonin and nonvertebral fracture risk even seemed to perhaps be U-shaped, with higher fracture risk at low and high serum levels than at mean levels.

The MrOS\(^9\) study also explored potential mechanisms such as BMD and fall risk behind the increased fracture risk. An inverse relationship between BMD and serum serotonin was found, indicating that the effect on fractures may be mediated by decreased bone biomechanical competence.

Besides the negative association of increasing serum serotonin with BMD, low serum serotonin levels were associated with an increased prevalence of prior falls, although no prospective data were reported. The association between serotonin and fall risk indicate that the central effect may be mediated via effects on postural control—in the opposite direction of the effect on BMD. As the effects of serum serotonin on BMD and risk of falls may be in opposite directions, they may negate each other.

Sex steroids are important to fracture risk because estradiol and testosterone may both increase BMD and thus reduce fracture risk, whereas testosterone may also increase muscle mass in men and thus potentially prevent falls and fractures. No analyses for sex steroids were performed in the MrOS study.\(^9\) The influence of these thus cannot be determined from the present study.\(^9\) The MrOS study examined effects of potential...
sarcopenia and reported a positive linear correlation between serum serotonin and hand-grip strength. Other sarcopenia markers (6-m walking speed test and appendicular lean mass) were not correlated with serotonin. Men with high serotonin values were stronger and had fewer falls but still had increased risk for incident fractures, nonvertebral osteoporotic fractures, and hip fracture. Because these measures for sarcopenia may be associated with sex steroid levels, in particular testosterone, the absence of measures of this may be less important.

The MrOS study adjusted for a number of important confounders including use of SSRIs and body mass index (BMI). However, unmeasured confounding may still exist. At present only the MrOS study thus suggests an association between serum serotonin and risk of fractures.

Despite the correlation between BMD and fracture risk, the low relative risk suggests that on a population level only a small proportion of fractures may be attributed to high serum serotonin, and the predictive value of serum serotonin for fracture prediction has not been validated in independent studies. For example, a recent cross-sectional study in men did not find any associations between prevalent fractures and serum serotonin. The latter study was smaller than the MrOS study, which to some degree may account for the absence of a relationship due to the risk of a type 2 error related to the magnitude of the relative risk of fracture associated with high serum serotonin.

Besides being present as a neurotransmitter in the gut and CNS, serotonin is also abundant in thrombocytes, and thrombocyte degradation may cause falsely elevated serotonin levels if blood drawing procedures are not performed correctly. Attention to sampling techniques and assays may thus be warranted. Intervening diseases and treatments with medications that may alter serotonin production or metabolism represent additional confounders that weaken the association between circulating serotonin and fracture incidence. Furthermore, serum serotonin only represents a fraction of the body’s serotonin, and may not be reflective of CNS serotonin because of the blood brain barrier, or of the effect of serotonin signaling from the CNS. Finally, no studies exist on whether modulating serotonin affects risk of fractures—and importantly the risk of falls. The increasing use of drugs that modulate serotonin signaling such as SSRIs and 5-HT receptors in, eg, diabetic gastroparesis, such as prucalopride, may give rise to concern regarding potential and actually proven association with risk of fractures besides those of the underlying disease, such as major depressive disorder and diabetes.

All these considerations add to the complexity of interpreting serum serotonin in relation to bone density and fracture risk. Consequently, at present caution is advised when interpreting the association between serum serotonin and fracture risk.

Future studies would need to focus on prospective fall risk associated with serum serotonin, longitudinal changes in BMD, potential effects of modulating serum serotonin levels, and potential effects of interacting with the 5-HT receptor.

**Disclosures**

All authors state that they have no conflicts of interest.

**References**