

Literature Review (September 2009)

Serotonin Production And Bone Health

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Introduction

Recent research on serotonin has suggested that serotonin has a negative impact on bone health hindering formation of new bone resulting in net loss. This information, in turn, brings into question the use of nutritional supplements that act as precursors to augment serotonin production. Concurrent to these publications other recent studies have been published which elucidate the possibility of new therapeutic roles for l-tryptophan, serotonin and melatonin.

L-Tryptophan history

L-tryptophan, one of the 20 essential amino acids, was first chemically isolated in 1901 by Sir Frederick Hopkins, better known for the isolation of glutathione and for his 1929 Nobel Prize. L-tryptophan serves as a precursor to niacin, serotonin and melatonin. It was formerly much more widely used as a nutritional supplement, prescribed primarily as a sleep aid and anxiolytic, both actions probably due to its ability to increase both serotonin and melatonin levels. A 1989 outbreak of eosinophilic-myalgia syndrome (EMS) that left about 1,500 people permanently disabled and killed 37 is still attributed to this widespread usage of l-tryptophan. Epidemiological studies linked the outbreak to l-tryptophan made by a specific Japanese producer employing genetically modified bacteria in the production process.¹ This explanation has provided a suitable etiology for the EMS outbreak though a recent 2005 paper offered another explanation for the EMS outbreak, which suggests that high doses of l-tryptophan affect histamine release that may in turn trigger EMS.² Sales of l-tryptophan were banned in the United States between 1991 and 2001 because of the EMS outbreak but have since been resumed.

During the years in which l-tryptophan was difficult to obtain, it became common to use another dietary supplement known as 5-Hydroxytryptophan (5HTP) instead. 5HTP is also a precursor to serotonin and some feel 5HTP acts more effectively than l-tryptophan because it is further along the pathway in the production of serotonin from l-tryptophan. Conversion of l-tryptophan to 5HTP is a rate-limiting step in the production of serotonin. Giving 5HTP skips this step and so nothing is lost to degradation by this enzyme and serotonin production can't be slowed. Furthermore, 5HTP crosses the blood-brain barrier easier than l-tryptophan.³ These same facts are also employed as arguments in favor of using l-tryptophan; 5HTP bypasses the body's ability to control serotonin levels.

The belief that serotonin is a benign substance that makes people happier permeates our culture and is likely due to the commercial promotion of antidepressant medications that increase serotonin. It is a widely accepted belief that both l-tryptophan and 5HTP ameliorate depression without significant negative side effects by increasing serotonin. The scientific literature now tells us we were wrong about serotonin not having adverse effects.

Serotonin and Bone

Current consensus in the literature suggests serotonin weakens skeletal bone. It is a reasonable assumption, although not yet scientifically proven, that regular usage of l-tryptophan or 5HTP may do the same. As other studies suggest that l-tryptophan may be beneficial in treating chronic pancreatitis, esophageal ulceration and liver cirrhosis, it is apparent that serotonin augmentation through supplementation requires careful analysis of risk versus benefit.

Initial indications that serotonin adversely affects bone appeared over a decade ago. A May 1998 article in *Lancet* reported on 8,239 Canadians treated for hip fracture comparing them against matched controls. Use of SSRIs increased the odds ratio of hip fracture to 2.4.⁴ Other types of antidepressants also increased hip fracture rates thus the mechanism remained unclear. Depression itself might have caused the increased rates, so might the drugs or the mechanism by which the drugs worked. Just a few years later, there was a clearer indication that increased serotonin levels were the contributing variable that weakened skeletal bone.

A paper by Dutch researchers published in August 2001 reported that both osteoblasts and osteocytes have receptors that bind serotonin.⁵ A 2001 article by Bliziotis and colleagues from the VA Hospital in Portland Oregon, reported that osteoblastic cells cultured in their lab responded to serotonin, increasing the effect parathyroid hormone had on them.⁶ Parathyroid hormone pulls calcium from the bone leaving the bone more prone to fracture. By March 2002 Bliziotis' team reported that using mice that lacked the serotonin transporter (5HTP) led to osteopenia in experiments.⁷ Serotonin played a role, but still unclear role, in bone health. In March 2005, Bliziotis went on to report that serotonin plays a role in bone accrual in growing skeletons and started questioning how these drugs affect children and adolescent bones.⁸ In October 2005 another Bliziotis' paper raised the concern that since the pharmacologic agents used to treat affective disorders target the serotonin system, attention should be given to what effects they might have on skeletal development. In other words, the overuse of SSRIs might contribute to our increasing risk of hip fracture.⁹

Though it was accepted that children suffering from depression have thinner bone density, consensus that SSRIs were to blame was lacking. Initial assumptions were that loss of bone density in children with depression was the result of other factors and not their treatment with pharmacologic agents that led to an increase in serotonin. As recently as April 2007, one paper still proposed other possible explanations:

“Physiologic factors, such as hypothalamic-pituitary-adrenal axis dysfunction and increased circulation of inflammatory cytokines, may adversely impact bone metabolism. In addition, behavioral factors, such as reduced physical activity and altered dietary intake (especially of bone-related nutrients such as calcium and vitamin D), may be implicated.”¹⁰

A few months later, the opinion began to consolidate as scientific research accumulated. A June 2007 article in the *Archives of Internal Medicine* reported on the bone density of women taking various types of antidepressants. The authors assessed SSRI use in a group of 2,722 older women. Those taking SSRIs had almost twice the yearly bone loss compared to those who had never taken an SSRI. The authors concluded:

“Use of SSRIs but not TCAs is associated with an increased rate of bone loss at the hip in this cohort of older women.”¹¹

A similar study appeared in the same issue of the *Archives of Internal Medicine* reporting on men. Analyzing data from 5,995 men, the authors found that the 160 men in the group who

used SSRIs had 3.9% lower bone density in the hips and 5.9% lower bone density in the lumbar spine. Men using other types of antidepressants such as trazodone hydrochloride or tricyclic antidepressants had no differences in bone density compared to nonusers. Other types of antidepressants had no apparent effect on bone density. These decreases approximate the bone loss seen in individuals prescribed steroids for extended periods.¹² This last piece of information gives us a sense of the magnitude of the problem as many practitioners have seen patients who have developed osteoporosis secondary to steroid use.

Steroids are the leading cause of medication-induced osteoporosis according to a 2005 article in the *Journal of Endocrinological Investigation*. The incidence of new fractures after one year of steroid therapy can be as high as 17%. These fractures are often asymptomatic and occur in 30-50% of patients using steroids for extended periods.”¹³

By February 2008 the papers being published were elucidating possible mechanisms by which serotonin contributed to bone loss and expressing greater concern about serotonin contributing to osteoporosis risk. Collett reported the identification of a particular serotonin receptor that mediated serotonin’s impact on bone formation and osteoporosis in aging women.¹⁴

A March 2008 paper that examined bone densities in 607 Australian women found that those taking SSRIs had lower bone mineral densities (BMD). The authors concluded:

“BMD among SSRI users was 5.6% lower at the femoral neck..., 6.2% lower at the trochanter...and 4.4% lower at the mid-forearm...than nonusers.”¹⁵

Again, these losses are similar in magnitude to those caused by long-term prednisone use making this relevant in clinical practice.

The loss in bone density resulting from SSRI use is independent of estrogen status. Decreased estrogen levels seen post hysterectomy, post menopause or with hormone blockade therapy for cancer will trigger an increased rate of bone loss. Hormonal replacement therapy does not cancel out the accelerated bone loss caused by SSRIs.¹⁶

In January 2009, a Dutch review reported that SSRI use is associated with both decreased bone density and also with an increase in fracture rates. Some of the increase in fractures was almost immediate occurring within the first 14 days of initiation of drug therapy.¹⁷ This immediate increase was unlikely to be a result of SSRIs weakening bone but more likely resulted from an increased risk of falling from SSRI use.¹⁸

The results from another line of research involving the Wnt signaling pathways and bone formation support the possible association of serotonin and bone loss. This was the discovery that the Wnt signaling pathways regulate bone activity. Wnt is a family of proteins that coordinate development and maintenance of body parts. One of the transmembrane proteins in this pathway, low-density lipoprotein receptor-related protein 5 (lrp5), helps regulate bone deposition and removal. Different mutations of the gene that code for lrp5 lead to either severe osteoporosis or the opposite, a condition known as high bone mass syndrome.

A February 2009 review tells us that while increased Wnt signaling strengthens bone, it weakens articular cartilage.¹⁹ This illustrates the complex role Wnt plays at regulating these processes. Another paper published in February described the state of knowledge as “exploding” and suggested that Wnt signaling did not affect the bone directly, as first thought, but did so indirectly by targeting duodenal enterochromaffin cells in the GI track and thereby regulating serotonin production.²⁰

By July 2009's edition of the journal *Bone*, the mechanisms underlying Wnt signaling and serotonin, at least for the moment, are to some degree defined. Current available data shows when serotonin binds to the serotonin 1-b receptor on pre-osteoblastic cells it inhibits the cell from developing into a full-fledged osteoblast. Osteoclasts, unlike osteoblasts, are not affected by the serotonin level and continue to reduce bone mass. Therefore, with less activity from osteoblasts and the same activity from osteoclasts, the bone density will only decrease as long as serotonin binds to the serotonin 1-b receptors. Lrp5 affects how much serotonin is produced in the intestine.²¹ Lrp5 interferes with serotonin production in the gut by blocking the enzyme that converts l-tryptophan to serotonin. Prior to this it had been thought that lrp5 simply inhibited osteoblasts directly via Wnt/beta-catenin signaling through their cell membranes. Exposure to serotonin slows bone cell growth. The more lrp5 in the gut, the less serotonin is made and the stronger the bones. Warden et al in a July 2009 *Bone* article described the magnitude of these changes in understanding as a paradigm shift.²²

The current state of knowledge suggests that we view SSRI use with caution in patients with low bone density or at increased risk for osteoporosis. By association we should wonder if l-tryptophan deserves the same caution. As lrp5 apparently reduces conversion of l-tryptophan to serotonin this concern may be needless. It remains unclear how this will play out in clinical practice. Will higher levels of l-tryptophan achieved through oral supplementation bypass the lrp5 affect on regulating conversion? Or will elevated lrp5 prevent conversion of the supplemental l-tryptophan preventing serotonin increases?

In recent years several interesting papers have suggested that l-tryptophan may have novel therapeutic uses. For example a 2005 paper in the *Journal of Pineal Research* suggested that the melatonin made in the gut from l-tryptophan is, "...highly protective...against the damage of both the stomach and the pancreas and accelerates the healing of chronic gastric ulcerations..."²³ There is ample justification to use l-tryptophan more often.

Final Thoughts

Though new details are being published almost weekly, there is still a long way to go before the interaction between these various controls over bone formation and mood are fully understood. Certainly, there is now adequate justification for hesitancy in adherence to the simplistic formula, "increasing serotonin makes people happy" employed to encourage usage of SSRIs.

Naturopathic medicine employs two key modes of thinking. One mode utilizes our knowledge and understanding of the inner mechanisms and rules that guide the body's function to judiciously select and apply therapeutic interventions that will steer the body toward proper function. The other mode falls back on that idea that nature heals and our role is simply to employ the techniques that stimulate this healing process.

It is important to differentiate between allopathic botanical medicine that uses herbs as drugs and naturopathic botanical medicine that uses herbs to stimulate healing and improve function. The same differentiation applies to nutrient supplementation. We may employ l-tryptophan "naturopathically" to heal gastric erosion yet when used to treat depression, our use might best be described as allopathic. L-tryptophan may be more "naturopathic" than 5HTP as it is still subject to the body's own feed back and regulatory mechanisms that control conversion to serotonin. It is too early to judge the possible effects of l- tryptophan or 5HTP on bone health because there have been no studies evaluating focused on this. Caution is certainly warranted

with these two supplements until more information is available. Those patients using SSRIs should be carefully evaluated for other fracture risk factors and steps taken to reduce them. Their bone densities should be monitored with the same vigilance we normally reserve for patients taking long-term steroids.

Although scientists describe paradigm shifts in the understanding of serotonin and Wnt signaling pathways, we are still far from fully understanding all the implications of artificially adjusting serotonin levels. Are we neglecting some of the older and simpler natural techniques that might push start the healing process? For example, could a week spent hiking in the mountains achieve a suitable shift in these chemicals comparable to supplementation with l-tryptophan?

An interesting paper to consider in light of this question was published in the July issue of *Environmental Health*. The authors report on the “effect of sunlight exposure on the cognitive function among depressed and non-depressed individuals.” After evaluating data on sunlight exposure in 16,800 people, the authors tell us that, “A dose-response relationship was found between sunlight exposure and cognitive function, and this relationship differed by depression status.” Depressed people were more than twice as likely to be sensitive to reduced sunlight than non-depressed people (odds ratio=2.58).²⁴ Translated into clinical terms, getting depressed people out into the sun helped them think more clearly.

In our rush to utilize new supplements and keep up with scientific developments, it’s easy to forget the simple therapeutic interventions of the naturopathic profession. Perhaps before we tell our next depressed patient that their cure is in upping their serotonin levels via drugs or supplements, we consider the advisement of a daily ambulation providing “helio” exposure?

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