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From drugs targeting serotonin pathways to the fracture risk

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ABSTRACT *The serotonin is connected to the bone homeostasis because the peripheral molecule stimulates bone loss and it has a positive bone mass effect by the neural central skeleton control. The drugs as selective serotonin reuptake inhibitors (SSRI) interfere in the serotonin pathways by displaying more serotonin to the bone. Thus the risk of fracture is augmented and clinical data pointed significantly deficit in the bone mineral density after long term use. Also, an increased risk of fall especially at the begging of the therapy is seen mainly related to cardiovascular events as arrhythmias, syncope, and hypotension. Nevertheless, the depression itself has a negative impact on bone mineral density and to the overall risk of fracture other potential mechanism are registered: vitamin D deficit, obesity, etc. The tools to assess the fracture risk are central Dual-Energy X-Ray Absortiometry and perhaps the bone turnover markers, but not currently plasma serotonin assay.*

Introduction

The serotonin or 5-hydroxytryptamine is a complex molecule synthesized from tryptophan with a double location and a double role: the brain monoamine stimulates the bone formation via neural control (also connected to the energy and appetite balance pathways via leptin or sympathetic nervous system functions) whiles the blood and bone 5-hydroxytryptamine (5-HT) causes bone loss. **(1,2 ,3)** The peripheral serotonin mainly originates from the neuroendocrine intestinal cells and it circulates into the blood at the level of platelets. The serotonin transporters are involved in serotonin uptake by thrombocytes. The second peripheral source is the bone itself. **(4)** The 5-HT transporters were found in osteoblasts and osteoclasts as well as the most important enzyme in the serotonin production tryptophan hydroxylase 1, and also the 5-HT receptors: type 2A in osteoblats, type 2B in osteclasts (regardless the cells level of maturation), and type 1B in both types of cells. **(5)** The drugs as those used in depression for instance selective serotonin reuptake inhibitors (SSRI) represent a common medication targeting the blood and bone serotonin transporters as well as similar ones from central neurons. They block the peripheral transporters thus increases the amount of serotonin to the bone. **(6)** By interspersing to the 5-HT pathways these drugs influence its level at the bone and the "crosstalk between skeleton and brain" via serotonin. **(7)** That is why SSRI and depression itself are regarded as a secondary cause of osteoporosis, a new comer in the playlist including causes of bone loss after the evidence based medicine proved it. **(8)**

General data

Serotonin assay

The clinical use of routinely testing serotonin is not yet completely understood since intra-normal ranges might be seen in patients under antidepressants or diagnosed with low mineral density as seen in menopausal osteoporosis. One of the major issues in assaying serotonin is its high variability with food meaning all kind of tryptophan sources as banana, avocado, etc that should be avoid two days before evaluation. Also medication as vasodilatators stimulates serotonin release from the plates or others as aspirin, reserpin interact with the monoamine metabolism**.** These should be stopped at least five days before the assay. **(9)** On the other, the current use of serotonin assessment as a potential bone turnover marker is not completely understood. The data from CALEX-family study showed that peripheral serotonin is negatively correlated to the weight, and potentially to the lumbar areal bone mineral density in premenopause, in opposite to postmenopause status where the correlation is positive with femoral areal bone mineral density. This study was not consistent with the similar skeleton observations in men**. (10)**

Fracture risk

The fragility (osteoporotic) fractures are caused by many factors but the main two we mention in this area are: the effects of SSRI on bone mineral density and the risk of fall. It seems that the bone density is affected after a longer period of time in a dose dependent pattern (also not all the studies found a low bone mineral density) while the risk of falling is more pronounced at the beginning of the SSRI therapy. (**6,11)** Current users SSRI have a twofold risk of fracture. **(12)** In postmenopause, according to the Women's Health Initiative Observational Study (including women with an average age of 64 years) there was no observation in significant bone mineral density changes for 3 years in persons with depression. The antidepressant drugs increased the fracture risk at the spine (HR=1.36; CI=1.14 to 1.63), but not at the hip or wrist. The higher risk was not correlated to a relevant decrease in the bone mineral density. **(13)**

The potential of fall is higher in patients with depression because of weight gain; co-dependence of alcohol, drugs, etc; the medication as antidepressants increases the risk of fall by associating cardiovascular events as arrhythmias. **(14)** The timing was also found to be correlated to fractures meaning that the risk of fall is greater in the first two weeks from starting the medication possible correlated with syncope or orthostatic hypotension. **(15)**

The fracture risk in interpreting the data from SSRI users has some potential confounding factors: the persons with depression may be at higher risk for hypercortisolemia, hypogonadism, obesity and binge eating behaviour, lack of

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physical exercise and sun exposure, augmented setting of the oxidative stress and inflammatory status, all of these been revealed as associated with fragility fractures. **(16)** Moreover, lower levels of 25-hydroxy vitamin D were found in InCHIANTI study as correlated with the depressive mood, hypovitaminosis D being a supplementary mechanism of fall risk. **(17)**

Another clue in interpreting the skeletal effects is that there is still a matter of debates which part is actually due to the depression itself is and which is caused by the medication against the mental illness. Overall, according to a meta-analysis of 23 studies a lower bone mineral density is seen in people with depression versus persons without the disease. The association is stronger in women than men, in premenopause versus postmenopause. **(18)** Another meta-analysis on 535 articles (especially 20 studies out of 33 selected papers) showed that major depression associates clinically relevant deficit of bone mineral density: for spine it was 4.73% lower than control, for total hip it was 3.53% more decreased, for femoral neck it was 7.32% lower. **(19)** Another meta-analysis of 2001 articles (including 35 studies with adequate data) pointed a strong correlation between the mental disease and osteoporosis (including the SSRI use and bone mineral density). **(20)** Applying the scale of depression or anxiety the higher scores increases the risk of osteoporotic fracture in men but not in women, according to The Hertfordshire Cohort Study. **(21)** Another potential confounder factor is the overlap between substance abuse disorders and the mood disorders that independently may be associated with osteoporosis. **(22)**

As diagnostic tools of fracture risk assessment we mention the central Dual-Energy X-Ray Absortiometry (DEXA) by providing the bone mineral density useful especially in persons under medication for a long time and menopausal women or women in hypo-estrogenic state. The Kangwha study found a statistically significant negative correlation between the stiffness indexes calculated based of heel quantitative ultrasound and depression elements but only in men, not in women. **(23)** The bone turnover markers vary with therapy. Depression involves an increased bone markers status correlated with the severity of the symptoms. The antidepressant medication may decrease the bone resorption markers and augment the bone formation markers as seen in one study in premenopausal women. This does not necessary predict the fracture risk. **(24)** Neither testing the plasma serotonin pointed no special use in order to point the fracture risk. **(25)** Others potential skeleton effects are registered in pregnant women taking SSRI who may associate children bone anomalies compare to non-consumers. In one study, the tibia speed of sound (as revealed by quantitative ultrasound) of the newborns from mothers taking SSRI was not statistically significant different from control but the length and the head circumference at birth was significantly lower. **(26)**

Conclusion

Based on serotonin pathways interferences, especially at the level of 5-hydroxitrytamine transporters, the depression and the use of selective serotonin reuptake inhibitors correlates with a higher risk of fracture. This underlies changes in bone mineral density but also in the risk of fall.

Conflict of interest: none

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