HORMONES 2013, 12(3):350-362

Review

The "depressive" face of osteoporosis and the "osteoporotic" face of depression

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ABSTRACT

Osteoporosis and depression are two chronic diseases that affect large population groups with great impact on morbidity, mortality and quality of life. An association between osteoporosis and depression has been described in the literature. Definitely, limited data suggest that osteoporosis may enhance depressive symptoms, while far more studies have shown that depression adversely affects bone density and increases fracture risk. However, neither causation nor a firm pathophysiological connection has been established. Thus the correlation of these diseases is still under research. This review comments on a plausible causative relationship and underlying mechanisms that might elucidate the link between two very common diseases. We describe the possible impact of osteoporosis on moods and the (better established) effect of depression on bone health. We also describe the effect of medication and review hormonal and cellular signals that may explain this effect.

Key words: Antidepressant medications, Causality, Depression, Falls, Fractures, Osteoporosis

INTRODUCTION

Osteoporosis is a chronic skeletal disease characterized by systemic impairment of bone mass and decline in bone strength resulting from micro-architecture deterioration. As a result, the propensity to fragility fractures of the vertebrae, wrist, hip and other skeletal sides is increased,[1-3] with fragility fractures inevitably augmenting morbidity and mortality among this population.[3-6] It may also generate chronic pain, which diminishes mobility and consequently the capacity for self-care, often creating a feeling of loss of independence and low self-esteem. All these adversely affect the patients' quality of life.[7-11] The financial burden of osteoporosis is substantial, taking into account both acute and rehabilitative care following osteoporotic fractures, while the societal burden is also aggravated by the decrease in health status.[12,13] In fact, by 2025, annual direct costs from osteoporosis are expected to reach approximately $25.3 billion, while the cost for fracture treatment in Europe alone is estimated to exceed 76 billion Euros by 2050.[13,14]

Depression is another chronic debilitating disease with high prevalence, characterized by changes in mood, self-attitude, cognitive functioning, sleep, ap-

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Received 11-02-2013, Accepted 04-06-2013

petite and energy level, which have a major impact on quality of life.[15] In general, depressive disorders are expressed by sadness that interferes with daily function and are often accompanied by decreased interest or pleasure in activities. The term depression is often used to refer to any of several depressive disorders including *major depressive disorder* (often called major depression or MDD), *dysthymia*, *depressive disorder not otherwise specified*, *depressive disorder due to a general physical condition* and *substance-induced depressive disorder.*[16] Major depression is a leading cause of disability worldwide, second only to hypertension, and the most common chronic condition encountered in general medical practice, while it will in all likelihood be the greatest cause of disability worldwide by 2020.[15,17,18] The exact pathophysiological mechanism is still being studied but the etiology is most probably multifactorial, involving heredity and psychosocial factors, changes in neurotransmitter levels and altered neuroendocrine function. Thus, diagnosis is based on medical history. Treatment usually involves drug administration, psychotherapy or both, and, occasionally, electroconvulsive therapy or phototherapy.[16]

Depression is correlated with osteoporosis substantially in literature, wherein weak support for the idea that osteoporosis and fractures cause depression is documented, while, in contrast, there is more evidence that depression (especially when treated with certain antidepressant medications) or other mood disorders, as anxiety and stress, have negative correlation with bone density and are associated with an increased risk of osteoporotic fractures.[19-22] When a link between two ailments is reported, an exploration of causation is mandatory. In the present case, the question arises whether depression leads to low bone density and fractures, or whether osteoporosis is the cause of depressive symptoms. The direction of the causative link is still controversial and the etiology remains unclear.[23] The aim of this article is to summarize the current evidence that may elucidate some pathophysiological aspects of this association (Figure 1).

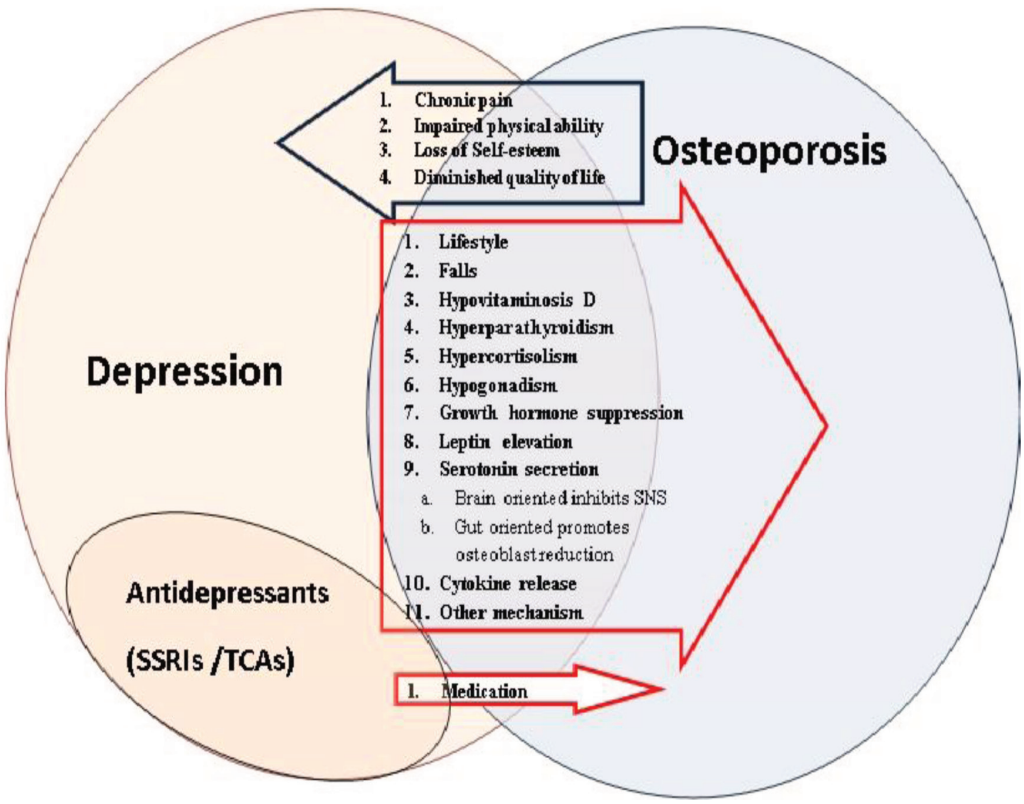

Figure 1. The bidirectional relationship of depression and osteoporosis (proposed mechanisms)

A. THE "DEPRESSIVE" FACE OF OSTEOPOROSIS

Chronic pain, in general, significantly impacts on patient-perceived health status. It adversely affects everyday activities, among which are personal relationships and work, thus evoking depressive symptoms.[24] Impaired physical activity and the inability to function in everyday life creates a sense of incapacity that may reduce self-esteem and the perception of well-being. In osteoporosis, chronic pain, which rises from deformities of skeletal, joint and musculo-tendineous structures,[9,25] leads to diminished quality of life.[7-11]

There is no solid evidence that osteoporosis per se leads to psychological illnesses and no proof that it can be the cause for depression. Studies, limited in numbers and weak in provision of conclusions, are however in accordance with physicians' impression that osteoporosis and fractures may lead to some degree of depression, as they affect the psychic sphere in many ways. Osteoporosis, even without co-existing clinical fractures, has been associated with the undesirable consequences of chronic pain, deformity, impaired physical ability, reduced social activity, loss of control, poor well-being and depressed mood, which overall lead to a reduced quality of life.[11,26,27] Thus, women with osteoporosis may present significantly higher levels of depressive symptoms and a corresponding higher prevalence of depression.[28]

The Multiple Outcomes of Raloxifene Evaluation (MORE) study showed increase of prevalence of depression among patients with osteoporosis and especially in postmenopausal women with vertebral fractures who exhibit much greater prevalence of depressive symptoms and probable depression compared to those without fractures while the number of fractures resulted in a proportionately worse "Geriatric Depression Scale" score.[29] Additionally, osteoporotic fractures, like hip fractures, promote depressive expressions, the frequency of which may range from 9% to 47%, and hip fracture patients may develop major depression even before being discharged from the hospital.[30]

The impact of osteoporosis on individual mental health has been studied, at a population level, by accessing patient reported outcomes (PRO) through validated questionnaires which explore quality of life, back pain, ability to function and anxiety and depressive symptoms that arise from a degree of incapacity that comes with the disease and an overall sense of ill-being.[31] The improvement of self-reported depressive symptoms mitigated by antiosteoporotic treatments that are recorded through such questionnaires could be mediated through improvement of the frequency and severity of back pain and movement limitations, as has been recorded.[32]

B. THE "OSTEOPOROTIC" FACE OF DEPRESSION

While limited literature supports the notion of depression being a direct complication of osteoporosis, quite a few studies have provided evidence that depression may lead to bone health deterioration and increased fracture risk in adults,[17,19,33-35] and could even affect peak bone mass in children and adolescents.[36] For more than a decade, the question has been posed as to whether depression is a major risk factor for osteoporosis, as a strong association between depression and osteoporosis has been revealed.[37]

Depression and Bone Mineral Density

Depression has been associated with lower bone mass,[37] but the results regarding this association differ between published studies and meta-analyses depending on the study design, evaluation of depression and other characteristics of the included population. Such results are summarized in different tables of many publications, as e.g. in those by Cizza et al.[23,38]

After adjustment for osteoporosis risk factors, Bone Mineral Density (BMD) is negatively associated with depressive symptoms in older patients.[38] This association has also been observed in patients with self-reported depression, in psychiatric populations, in adult men and pre-, peri- and postmenopausal women and even in children and adolescent patients.[20,33,34,37-43] In the latter population, two quite recent studies drew contradictory conclusions: in one only adolescent boys with MDD presented with statistically lower hip bone density compared to controls,[44] while in the other depressive symptoms had a deleterious effect on bone accrual among adolescent girls.[45] In young patients, lower density of trabecular but not cortical bone was shown.[20] Since there is great interest regarding the effect of depressive disorders on bone formation and peak bone mass attenuation, larger studies elucidating this subject should be implemented.

Low BMD is prevalent even at very early stages of major depression.[34,46] In a meta-analysis, Yirmiya and Bab specified that depressed individuals display lower BMD in the spine, hip and forearm, while a stronger association is observed for premenopausal than for postmenopausal women.[47] In another meta-analysis addressing the correlation of depression and bone density, Wu et al. showed a pooled lower BMD at the spine and hip for depressed compared to non-depressed groups.[35] Women diagnosed by a psychiatrist, and not those diagnosed by self-rating questionnaires, displayed significantly low BMD,[47] even though some authors relate low BMD with depression diagnosed by self-report questionnaires (based on the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria).[33]

Only a minority of studies have failed to demonstrate lower BMD in patients with depression.[48,49] The majority of studies, as described above, correlate depression with low bone density, and a study assessing determinants of osteoporotic fractures in primary care suggests that depression can be considered as a predisposing factor that shows clinical significance and magnitude of impact similar to other established risk factors for osteoporosis.[50] In an endeavor to provide an explanation regarding the inconsistency in association between depression and BMD in some studies, Heany and Warden conclude that differences in population or diagnostic assessments, the effect of medications and/or other non-measured confounders may be responsible.[51]

Depression and markers of bone metabolism

In some studies, depressed patients show increased urinary levels of bone resorption markers[46,47] and serum osteocalcin, parathyroid hormone (PTH) and C-terminal telopeptide (CTX),[52] this probably reflecting increased bone remodeling, while others provide evidence of higher cortisol excretion along with lower serum osteocalcin concentrations and urinary excretion of deoxypyridinoline.[20] In a recent study, bone turnover markers, parathyroid hormone and Receptor Activator for Nuclear Factor B ligand were significantly higher in depressed patients compared with controls, while serum levels of 25-hydroxivitamin D and osteoprotegerin were significantly lower.[42] However, there are also reports that were unable to establish any differences in cortisol levels in either pre- or postmenopausal women with depression.[42,46] Moreover, antidepressant therapy may alter markers of bone metabolism: in a study treating patients with escitalopram 10 mg/day, increased bone formation and decreased bone resorption in premenopausal women with major depression was revealed via marker measurements.[53]

Depression and falls

Falls are the seventh leading cause of death in older persons and depression is among their intrinsic causes.[54,55] Data summarized in the American Geriatrics Society guidelines suggest that depression confers a higher mean relative risk for falls (2.2) than cognitive impairment (1.8) or age of 80 and older (1.7).[30] The MOBILIZE Boston Study showed that the association of depressive symptoms with fall risk in older adults is mediated, in part, by chronic pain.[56] In addition to the above, some antidepressants (especially selective serotonin reuptake inhibitors (SSRIs) and possibly tricyclic antidepressants (TCAs)) contribute to falls, perhaps through sedation, insomnia and impaired sleep, nocturia, impaired postural reflexes and increased reaction times, orthostatic hypotension, cardiac rhythm and conduction disorders, movement disorders and/or other mechanisms.[57] Interestingly, depression following fractures may also be a risk factor for future falls,[58] which may lead to future fractures.

A bidirectional relationship of depression with falls proposes the mechanism of excessive fear of falling, which, through impairment of gait and balance, mediated through cognitive, sensory and motor pathways, leads to further increase in falls risk.[59]

Depression and fractures

Only a few studies have failed to confirm increased fracture rates in patients with depression.[60] The majority draw the conclusion of augmented risk of osteoporotic fractures, especially when antidepressant medications are being taken. Indicatively, women with depression present a roughly 40% increase in risk for non-vertebral fractures compared to controls for both pre- and postmenopausal mentally distressed women.[21,61,62] Depression has been identified as a predisposing factor for osteoporotic fractures in the primary care setting[49] and a predictive factor for hip

fractures, even after adjustment for antidepressant medication use,[19,63] with a hazard ratio of 1.9.[30] It is suggested that women with current depression or a past medical history might be at an increased lifetime risk for fractures because of the severity of their bone density losses.[20] Depression also seems to affect fracture healing: in a study of 55 patients with hip fracture, 69.1% had depression as diagnosed by respective questionnaires. Different functional recovery after surgery was recorded for depressed versus non-depressed subjects in this study.[64]

Antidepressants and fracture risk

The use of psychotropic medications, including anticonvulsants, barbiturates, narcotics and neuroleptics, has been associated with osteoporosis and increased fracture risk, especially in the elderly.[37,65-71] In the Study of Osteoporotic Fractures, depression, per se, as well as SSRIs were associated with increased rates of bone loss at the hip, when adjusted for potential confounders. This was not evident for TCAs in this study,[65,66] by contrast with other studies.[37] SSRIs have collectively been associated with osteoporosis and fractures.[37,67,68] A quite recent meta-analysis implicates the use of these agents with as much as a twofold increase in fracture risk, even after adjustment for potential confounders, with a dose-response relationship for SSRIs and an effect linked to the affinity of each SSRI for the serotonin transporter system. The increase in risk is expected to be higher within 1 month after initiation for tricyclics and 8 months for SSRIs and diminishes in the year following discontinuation.[69] Antidepressants, as previously mentioned, also increase the likelihood of falls, further aggravating the risk for fractures, thus providing one plausible causative connection between depression and osteoporotic fractures. Compared to non-SSRI users, serotonin reuptake inhibitors increase the relative risk of fracture by 72%.[69] Thus, recommendations have been issued for routine skeletal evaluation and timely antiosteoporotic therapy for patients with depressive disorders especially when SSRI treatment is prescribed.[70] As also mentioned above, less evidence connects tricyclic antidepressants (TCAs), benzodiazepines, valproate or other psychotropics with diminished bone health.[37,65-68] Risk assessment for osteoporosis per antidepressant therapeutic area has been estimated and osteoporotic fracture rates are increased two-fold with SSRIs, marginally increased with TCAs and possibly decreased with lithium.[67,71] A risk assessment per medication category provides an odds ratio (95% Confidence Intervals) of 1.45 (1.32 to 1.59) for SSRIs, 1.18 (1.10 to 1.26) for Carbamazepine, 1.15 (1.07 to 1.24) for Non-SSRIs (e.g., tricyclics, atypicals), 1.10 (1.04 to 1.16) for Benzodiazepines and 0.63 (0.43 to 0.93) for Lithium.[67]

A connection has been proposed between an anabolic effect of Glycogen Synthase Kinase (GSK)-3[beta] inhibition and the use of lithium: this would imply exertion of action through the Wnt/beta-catenin signaling in the skeleton. Of note, all of the major bone cell lines (osteoblasts, osteoclasts and osteocytes) possess a functional 5-hydroxytryptamine transporter (5-HTT) that is highly specific for 5-HT uptake as well as functional receptors for 5-HT. Thus, the SSRIs seem to have direct anti-anabolic skeletal effects which are attributed to the pharmacological inhibition of 5-HTT.[71]

In summary, evidence for a direct and an indirect (through medication) effect of depression on bone health has accumulated suggestive of bone mineral density decrease, falls sustainability and increased fractures rate in patients with depression.

A RELATIONSHIP IN BOTH SEXES?

Most of the literature that correlates osteoporosis with depression has derived from studying female populations, since both osteoporosis and depression are more prevalent in women. Nevertheless, osteoporosis has recently been recognized as an major cause of morbidity for the male sex as well, while unipolar depression, even though not as frequent as in women, still affects approximately one in ten men.[72] According to some authors the correlation between BMD and major depressive symptoms is stronger in women compared to men.[47] Others report that depressive symptoms are not associated with BMD in community-dwelling older men,[73] nor is fractures incidence increased.[62] By contrast, in population-based studies, an association of major depressive episode with bone mineral density (BMD) in young and older male adults was described.[74-76] The observation of increased bone loss in men with depression[37,65] and of an almost triple relative risk for the development of osteoporosis, compared to mentally healthy men,[77]

may provide further evidence for a positive relation of the two diseases in men, as established in women, and recommend that older men with depression be prompted to undergo screening for osteoporosis.[76] On the other hand, as regards adolescents, a recent study proved evidence of statistically lower BMD only in teenage boys, an association not observed in girls, while in another, depressive symptoms had a deleterious effect on bone accrual among adolescent girls.[44,45] The statistical power of the referred studies should be considered.

WHY DO DEPRESSED PEOPLE DEVELOP OSTEOPOROSIS?

1. Lifestyle

It is important to stress that, since modern populations are increasingly overfed, malnourished, sedentary, sunlight-deficient, sleep-deprived and socially-isolated, these changes in lifestyle each contribute to poor physical health and affect the incidence and treatment of depression.[78] According to this observation, such an unhealthy way of life, which may be observed particularly in severe cases of depression, could lead to low bone density and a susceptibility to fractures. More specifically, patients with severe depression are usually more prone to a sedentary lifestyle, low calcium intake diet, physical inactivity,[79] tobacco abuse,[80] excessive alcohol intake (>3 units per day),[81] and have a deteriorated quality of life.[82] Increased PTH and a low vitamin D (secondary hyperparathyroidism) may be a consequence of poor diet and lack of exposure to sunlight.[83]

2. Hormonal influences

It is suggested that, at a cellular level, the brain may control bone remodeling through genetic, molecular and physiological pathways, while, as with all other homeostatic functions, bone remodeling is under the control of the hypothalamus, thus osteoporosis should be considered a neuroskeletal disease.[84] Many changes in hormonal pathways which cross-interfere between bone and the brain, such as the decrease of estrogen and testosterone levels,[85] excess secretion of cortisol[38] or inflammatory cytokines[34, 86] have been implicated (Figure 2).

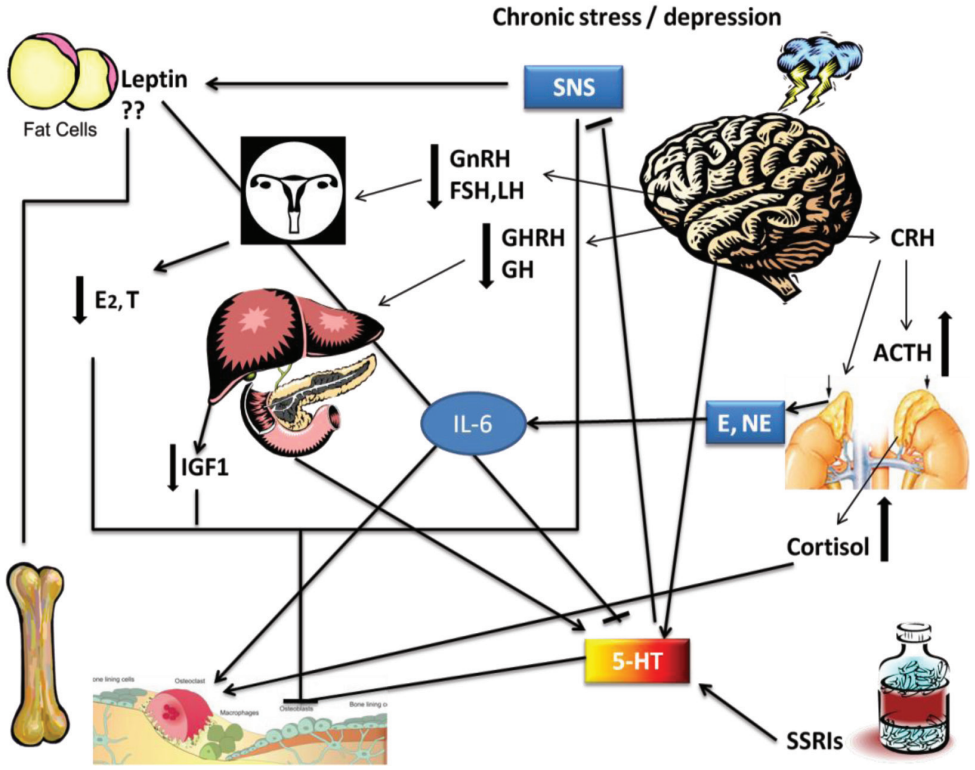

Figure 2. Suggested osteal-encephalic interactions in depression. The two colors of the 5-HT box represent its dual origin which leads to different mechanisms of action.

The role of Gonadal hormones, Growth Hormone, Cytokines and Cortisol

According to a suggested pathophysiologic mechanism, depression leads to excessive activity of the hypothalamic-pituitary-adrenocortical and sympathoadrenal axes,[37,48,71] with increased Corticotropin-Releasing Hormone (CRH) production which provokes higher ACTH and consequently cortisol secretion,[20] and suppression of the gonadal and somatotrophic axes with decrease of Growth Hormone-Releasing Hormone (GHRH) and Gonadotrophin-Releasing Hormone (GnRH) production which suppresses the secretion of GH and gonadal steroids, respectively. CRH also stimulates catecholamine release, inducing interleukin-6 production. The hyperactivity of the hypothalamo-pituitary-adrenal and sympathoadrenal axes, together with the suppression of the somatotrophic and gonadal axes, results primarily in decreased bone formation, ultimately leading to net bone loss.[72] In a minority of studies this bone loss has not been proven.[48]

Depression subtypes may have different effects on bone health

Depression subtypes may exert different effects on the Hypothalamus-Pituitary-Adrenal axis resulting in various degrees of endogenous cortisol suppression.[87,88] Moreover, different clinical subtypes of depression are associated with different circadian endocrine profiles and metabolic parameters.[89] Further research to evaluate the impact of different degrees/subtypes of depressive disorders on bone metabolism may be useful.

The role of Serotonin and the Sympathetic Nervous System

Serotonin modifies psychological and behavioral functions such as mood and anxiety and is an important neurotransmitter which plays a key role in the pathophysiology of psychiatric illnesses, like depression. Serotoninergic pathways may also play an important role in bone through 5-HT signaling or through some other mechanism. In consequence, depression and antidepressant medications may influence bone health through 5-HT signaling.[49] Serotonin (5-HT) is produced in the brain and the gastrointestinal tract, a portion of which is resorbed by platelets. 5-HT exhibits separate central and peripheral functional identities.[90] Due to the blood-brain barrier there is isolation in function of either fraction. 5-HT receptors have been identified in all the major bone cell types (osteoblasts, osteocytes and osteoclasts), and stimulation of these receptors influences bone cell activities, some studies showing stimulatory effects on bone formation and others showing inhibitory effects.[91] It seems that 5-HT acts both indirectly and directly, depending on its origin. There is a direct effect of gut-oriented 5-HT which promotes reduction in osteoblast proliferation.[92] Regarding brain-produced serotonin, this is released at neuronal synapses. Serotonin-producing neurons of the raphe nuclei project to the ventromedial (VMH) hypothalamic nuclei, decreasing the activity of the sympathetic nervous system (SNS), an inhibitor of bone mass accrual.[92]

There is even greater confusion when one tries to use the above data in serotonin changes that take place in major depression and through the action of SSRIs, where perhaps a central decrease of 5-HT results in increased SNS activity. Depression is associated with excessive adrenergic activity and a consequent increase in bone norepinephrine levels accompanied by restrained bone formation resulting from reduced osteoblast number and skeletal deficiency, suggesting a role for the sympathetic nervous system in skeletal effects of depression.[93] SSRIs may also interfere with 5-HT uptake by bone.[81, 90]

It has been proposed that there is a dual effect of 5-HT on bone metabolism with anabolic action from the brain-derived substance (which acts through inhibition of the sympathetic tone) and catabolic action from the gut-produced circulating 5-HT (which acts directly on bone cells through LRP5, an atypical member of the low-density lipoprotein receptor family),[94] and this could determine the basis for understanding the effects SSRIs have on bone health. It also introduces the Wnt pathway in the pathophysiology of depression-induced skeletal changes. Wnt serves as a stimulus of the proliferation of mesenchymal stem cells and the commitment of these cells into osteoblasts, preventing their differentiation to chondrocytes and adipocytes. It also increases the mineral apposition and bone formations rate and stimulates the production of osteoprotegerin, repressing osteoclast differentiation and function. Wnt activity is inhibited by sclerostin and

Dkk1, both secreted by late OBs and osteocytes. Dkk1 expression is increased by Wnt activity, establishing a negative feedback loop. Thus, the Wnt signaling pathway increases bone formation and represses bone resorption.[95,96] Mounting evidence suggests a role of 5-HT in mediating the complete skeletal effects of LRP5, which represents a significant paradigm shift from the traditional view that LRP5 located on the cell surface membrane of osteoblasts exerts direct skeletal effects via Wnt/beta-catenin signaling. It is of note, however that comparison of patients with carcinoid syndrome and elevated serotonin production with patients with carcinoid syndrome without elevated serotonin production revealed no differences in bone turnover markers.[97] Whether this observation questions the clinical relevance of serotonin, produced in the intestinal tract, in the control of human bone turnover or whether it is related to different effects of serotonin derived from carcinoid tumors needs further elucidation.

The role of leptin

Evidence indicates that leptin acts centrally, through its receptor (Lepr), expressed in serotonin-producing neurons of the raphe nuclei, decreasing the expression of tryptophan hydroxylase 2 (Tph2), the gene encoding the initial enzyme for serotonin biosynthesis.[37,92] Thus, leptin regulation of bone metabolism and bone mass may be mediated through inhibition of nuclear serotonin synthesis.[98]

Other data on leptin, however, suggest that it plays an anabolic role in bone formation and, at the serum level, its administration increases circulating insulin-like growth factor 1 (IGF-1), osteocalcin, osteoprotegerin (OPG) and receptor activator of NFkB ligand (RANKL).[99] The P.O.W.E.R. study showed 25% higher leptin levels, with a nocturnal rise, in community-dwelling premenopausal women with major depression. According to the authors, this may be secondary to activation of the sympathetic nervous system, which is known to stimulate leptin secretion and contribute to the development of osteoporosis in women with MDD.[100] Leptin levels, however, have failed to associate with bone mineral density or the risk of fracture in humans.[99,101] Regarding this point, namely the involvement of leptin in bone loss in humans with depression, the literature is as yet unclear.

Vitamin D and parathyroid hormone

Vitamin D insufficiency and concurrent hyperparathyroidism are known predisposing factors for osteoporosis.[102] Some studies,[103,104] but not others,[105] have linked low vitamin D levels with depression. No association of depression and PTH has been shown in most,[103-105] but not all cases.[41] However, very recent reviews associate primary hyperparathyroidism with depression and link parathyroidectomy with symptom alleviation.[106] Given the fact that PTH receptors have been found in the brain, in hypothalamic, limbic and sensory brain regions that potentially exert an influence on the neuroendocrine system,[107] one could speculate that chronically elevated PTH levels may have a direct effect on the nervous system, thus affecting moods. This speculation is subject to further research.

On the other hand, an increase in bone remodeling, independent of vitamin D deficiency, may induce calcium release and inhibition of parathyroid hormone secretion in depressive disorders.[108]

Since this field is not well elucidated, no pathophysiologic mechanism to link depression and osteoporosis through vitamin D can be proposed at the moment.

Table 1 and Figures 1 and 2 briefly depict the possible mechanisms expounded regarding a depression-osteoporosis association.

E. THE FRAX® SCORE AND DEPRESSION?

The FRAX® tool has been developed by the World Health Organization to evaluate patients' fracture risk. It is based on individual patient models that integrate the risks associated with clinical risk factors as well as bone mineral density (BMD) at the femoral neck (FRAX® WHO Fracture Risk Assessment Tool homepage).

There is no data regarding possible incorporation of depression (or other independent fracture risk factors). Perhaps this is because of the inconsistency of data between various studies. For example, in a study assessing 5-year incidence rates and determinants of osteoporotic fractures in primary care.[50] Although the FRAX® score was a reliable indicator, depression was an independent risk factor for fracture in women but

Table 1. Proposed pathophysiologic links between depression and bone deterioration

Poor lifestyle, tobacco and alcohol abuse, physical inactivity, dietary imbalances
Hormones • **Gonadal hormones.** Suppression due to chronic stress • **GH**. Suppression due to chronic stress • **Cortisol**. Excessive secretion due to hyperactivity of the hypothalamicpituitary- adrenocortical axis • **Leptin**. Not adequate data to support definite involvement. • **Vitamin D** and **PTH.** Depression linked with hyperparathyroidism, and low vitamin D levels. No association of depression and PTH in majority of studies.
Sympathetic Nervous System. Inhibitor of bone mass accrual. Excessive activity in depression.
Serotonin a. gut-derived: direct effect on bone, promoting reduction in osteoblast proliferation b. brain-derived: indirect effect on bone, through decrease of the activity of the sympathetic nervous system. In depression, brain 5HT levels fall. SSRIs may increase the direct effect on osteoblasts.
Cytokines. Stimulated, by CRH, production of IL-6

GH: Growth hormone, PTH: Parathyroid hormone, 5HT: Serotonin, SSRI: Selective Serotonine reuptake inhibitor, CRH: Corticotropin releasing hormone, IL: interleukin

not in men. Thus different methodology, inclusion criteria and treatment options may have made the use of depression in this tool impractical.

In the authors' opinion, since the use of the FRAX score for clinical assessment of osteoporosis is gaining ground, further research work should be performed evaluating the role of depression on the FRAX® score and its overall significance as independent predictive marker.

F. AVAILABLE GUIDELINES

According to recent recommendations of the Canadian Network for Mood and Anxiety Treatments (CANMAT) task force for the management of patients with mood disorders and select co-morbid medical conditions: [18]

1. The massively growing body of research on mood disorders and their effect on bone health suggests that this relationship is complex, and interpreting these findings has proved to be challenging. Patients age >40 with long-term SSRI exposure (>2 years) should be routinely screened for bone density via dual-energy X-ray absorptiometry (level 2).

2. The data related to long-term use of some mood stabilizers are more definitive, however, and we know that exposure is directly related to decreased BMD. Patients receiving long-term exposure to these medications should be routinely screened for bone density (level 1).

3. For adults age >50 who are at moderate risk of vitamin D deficiency, supplementation with 800 to 1000 IU (20 to 25 mcg) of vitamin D3 daily is recommended (level 2).

CONCLUSIONS

The majority of studies and meta-analyses provide evidence of an unfavorable effect of depression on bone health, which is likely to come about via more than one mechanism, suggesting that depression is a risk factor for osteoporosis and fractures. Additionally, patients with osteoporosis suffer the mental consequences of this chronic disease. The relationship is not only limited to postmenopausal women, who tend to be the focus of our interest when we discuss osteoporosis and fractures, but also involves men and young populations. However, because studies and meta-analyses use different diagnostic criteria, populations and methods of analysis, they may provide data that tend to be controversial and conflicting. It is therefore evident that the need for clinical trials to evaluate the effect of different types of depressive disorders as well as the impact on specific populations still exists.

Until then, we strongly believe that psychiatrists should be encouraged to provide patients with depression lifestyle modification instructions in order to improve bone health and avoid falls, while selected patients with depression should be evaluated for osteoporosis. We also agree with Haney et al. that at least SSRIs should be considered medications that contribute to osteoporosis and consequently SSRI users should be screened accordingly.[109]

ACKNOWLEDGEMENTS

We wish to thank Professor Richard Eastell for his productive review and annotation of the manuscript and his recommendations for enrichment of the text and journal targets.

CONFLICTS/DISCLOSURES

The authors state that no conflict of interest exists and this manuscript reflects solely their opinion as specialized endocrinologists, practicing in their private Medical Office.

REFERENCES

1. Rachner TD, Khosla S, Hofbauer LC, 2011 Osteoporosis: now and the future. Lancet 377: 1276-1287.
2. Cummings SR, Melton LJ, 2002 Osteoporosis I: epidemiology and outcomes of osteoporotic fractures. Lancet 359: 1761-1767.
3. Johnell O, Kanis J, 2005 Epidemiology of osteoporotic fractures. Osteoporos Int 16: Suppl 2: 3-7.
4. Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA, 1999 Mortality after all major types of osteoporotic fracture in men and women: an observational study. Lancet 353: 878-882.
5. Sambrook P, Cooper C, 2006 Osteoporosis. Lancet 367: 2010-2018.
6. Browner WS, Pressman AR, Nevitt MC, Cummings SR,1996 Mortality following fractures in older women. The study of osteoporotic fractures. Arch Intern Med 156: 1521-1525.
7. Papaioannou A, Kennedy CC, Ioannidis G, et al, 2009 The impact of incident fractures on health-related quality of life: 5 years of data from the Canadian Multicentre Osteoporosis Study. Osteoporos Int 20: 703-714.
8. Salaffi F, Cimmino MA, Malavolta N et al, 2007 The burden of prevalent fractures on health-related quality of life in postmenopausal women with osteoporosis: the IMOF study. J Rheumatol 34: 1551-1560.
9. Nevitt M, Ettinger B, Black D, et al, 1998 The association of radiographically detected vertebral fractures with back pain and function: a prospective study. Ann Intern Med 128: 793-800.
10. Cooper C, Jacob F, Chinn C, et al, 2008 Fracture incidence and changes in quality of life in women with an inadequate clinical outcome from osteoporosis therapy: the Observational Study of severe Osteoporosis (OSSO). Osteoporosis Int 19: 493-501.
11. Gold DT, Shipp KM, Lyles KW, 1998 Managing patients with complications of osteoporosis. Endocrinol Metab Clin North Am 27: 485-496.
12. Becker DJ, Kilgore ML, Morrisey MA, 2010 The societal burden of osteoporosis. Curr Rheumatol Rep 12: 186-191.
13. Dempster DW, 2011 Osteoporosis and the burden of osteoporosis-related fractures. Am J Manag Care 17: Suppl 6: 164-169.
14. Kanis JA, Johnell O, 2005 Requirements for DXA for the management of osteoporosis in Europe. Osteoporos Int 16: 229-238.
15. Pratt LA, Brody DJ, 2008 Depression in the United States household population, 2005-2006. NCHS Data Brief 7: 1-8.
16. http://www.merckmanuals.com/professional/psychiatric_disorders/mood_disorders/depressive_disorders.html. Last full review/revision December 2009 by William Coryell, MD. Content last modified December 2009.
17. Whooley MA, Simon GE, 2000 Primary care: Managing depression in medical outpatients. N Engl J Med 343: 1942-1950.
18. Ramasubbu R, Taylor VH, Samaan Z, et al, 2012 The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and select comorbid medical conditions. Ann Clin Psychiatry 24: 91-109.
19. Mussolino M, 2005 Depression and Hip Fracture Risk: The NHANES I Epidemiologic Follow-Up Study. Public Health Reports 120: 71-75.
20. Michelson D, Stratakis C, Hill L et al, 1996 Bone mineral density in women with depression. N Engl J Med 335: 1176-1181.
21. Gold DT, Solimeo S. 2006 Osteoporosis and Depression: a historical perspective. Curr Osteoporos Rep 4: 134-139.
22. Erez HB, Weller A, Vaisman N, Kreitler S, 2012 The relationship of depression, anxiety and stress with low bone mineral density in post-menopausal women. Arch Osteoporos 7: 247-255.
23. Cizza G, Primma S, Coyle M, Gourgiotis L, Csako G, 2010 Depression and osteoporosis: a research synthesis with meta-analysis. Horm Metab Res 42: 467-482.
24. Reid KJ, Harker J, Bala MM et al, 2011 Epidemiology of chronic non-cancer pain in Europe: narrative review of prevalence, pain treatments and pain impact. Curr Med Res Opin 27: 449-462.
25. Uebelhart B, Rizzoli R, 2005 Osteoporosis and pain or is osteoporosis painful? Rev Med Suisse 1: 1662-1165.
26. Salaffi F, Cimmino MA, Malavolta N, et al, 2007 The burden of prevalent fractures on health-related quality of life in postmenopausal women with osteoporosis: the IMOF study. J. Rheumatol 34: 1551-1560.
27. Adami S, Maugeri D, Toscano V, et al, 2011 Baseline characteristics of the population enrolled in the Italian Observational Study on Severe Osteoporosis (ISSO). Clin Exp Rheumatol 29: 477-484.
28. Coelho R, Silva C, Maia A, et al, 1999 Bone mineral density and depression: a community study in women. J Psychosom Res 46: 29-35.
29. Silverman SL, Shen W, Minshall ME, Xie S, Moses KH, 2007 Prevalence of depressive symptoms in postmenopausal women with low bone mineral density and/

or prevalent vertebral fracture: results from the Multiple Outcomes of Raloxifene Evaluation (MORE) study. J Rheumatol 34: 140-144.
30. Kamholz B, Unützer J, 2007 Depression after hip fracture. J Am Geriatr Soc 55: 126-127.
31. The EuroQol Group, 1990 EuroQol -- a new facility for the measurement of health-related quality of life. Health Policy 16: 199-208.
32. Aloumanis K, Karras D, Drossinos V, Korelis E, Polydorakis A, 2011 fracture incidence, quality of life, and back pain during 18-months treatment with teriparatide in greek postmenopausal women with osteoporosis: results from the european forsteo observational study. J Osteoporos 2011: 2011: 510398.
33. Jacka F, Pasco J, Henry M, et al, 2005 Depression and bone mineral density in a community sample of perimenopausal women: Geelong Osteoporosis Study. Menopause 12: 88-91.
34. Eskandari F, Martinez P, Torvik S, et al, 2007 Low Bone Mass in Premenopausal Women With Depression. Arch Intern Med 167: 2329-2336.
35. Wu Q, Magnus JH, Liu J, Bencaz AF, Hentz JG, 2009 Depression and low bone mineral density: a meta-analysis of epidemiologic studies. Osteoporos Int 20: 1309-1320.
36. Weller EB, Weller RA, Kloos AL, Hitchcock S, Kim WJ, Zemel B, 2007 Impact of depression and its treatment on the bones of growing children. Curr Psychiatry Rep 9: 94-98.
37. Cizza G, Ravn P, Chrousos GP, Gold PW, 2001 Depression: a major, unrecognized risk factor for osteoporosis? Trends Endocrinol Metab 12: 198-203.
38. Robbins J, Hirsch C, Whitmer R, Cauley J, Harris T, 2001 The association of bone mineral density and depression in an older population. J Am Geriatr Soc 49: 732-736.
39. Schweiger U, Deuschle M, Korner A, et al, 1994 Low lumbar bone mineral density in patients with major depression. Am J Psychiatry 151: 1691-1693.
40. Halbreich U, Rojansky N, Palter S, et al, 1995 Decreased bone mineral density in medicated psychiatric patients. Psychosom Med 57: 485-491.
41. Dorn LD, Susman EJ, Pabst S, Huang B, Kalkwarf H, Grimes S, 2008 Association of depressive symptoms and anxiety with bone mass and density in ever-smoking and never-smoking adolescent girls. Arch Pediatr Adolesc Med 162: 1181-1188.
42. Atteritano M, Lasco A, Mazzaferro S, et al, 2011 Bone mineral density, quantitative ultrasound parameters and bone metabolism in postmenopausal women with depression. Intern Emerg Med : 2011 May 17. [Epub ahead of print]
43. Erez HB, Weller A, Vaisman N, Kreitler S, 2012 The relationship of depression, anxiety and stress with low bone mineral density in post-menopausal women. Arch Osteoporos 7: 247-55.
44. Fazeli PK, Mendes N, Russell M, Herzog DB, Klibanski A, Misra M, 2013 Bone density characteristics and major depressive disorder in adolescents. Psychosom Med 75: 117-123.
45. Dorn LD, Beal SJ, Kalkwarf HJ, Pabst S, Noll JG, Susman EJ, 2013 Longitudinal impact of substance use and depressive symptoms on bone accrual among girls aged 11-19 years. J Adolesc Health 52: 393-399.
46. Yazici KM, Akinci A, Sutcu A, Ozcakar L, 2003 Bone mineral density in premenopausal women with major depressive disorder. Psychiatry Res 117: 271-275.
47. Yirmiya R, Bab I, 2009 Major depression is a risk factor for low bone mineral density: a meta-analysis. Biol Psychiatry 66: 423-432.
48. Amsterdam JD, Hooper MB, 1998 Bone density measurement in major depression. Prog Neuro-Psychopharmacol Biol Psychiatry 22: 267-277.
49. Malik P, Gasser RW, Moncayo R, et al, 2013 Bone mineral density and bone metabolism in patients with major depressive disorder without somatic comorbidities. Prog Neuropsychopharmacol Biol Psychiatry 44: 58-63.
50. Lapi F, Simonetti M, Michieli R, et al, 2012 Assessing 5-year incidence rates and determinants of osteoporotic fractures in primary care. Bone 50: 85-90.
51. Haney EM, Warden SJ, 2008 Skeletal effects of serotonin (5-hydroxytryptamine) transporter inhibition: Evidence from clinical studies. J Musculoskelet Neuronal Interact 8: 133-145.
52. Herrán A, Amado JA, Garcia-Unzueta MT, et al, 2000 Increased bone remodeling in first-episode major depressive disorder. Psychosom Med 62: 779-782.
53. Aydin H, Mutlu N, Akbas NB, 2011 Treatment of a major depression episode suppresses markers of bone turnover in premenopausal women. J Psychiatr Res 45: 1316-1320.
54. Morley JE, 2007 Falls-where do we stand? Mo Med 104: 63-67.
55. Byers AL, Sheeran T, Mlodzianowski AE, Meyers BS, Nassisi P, Bruce ML, 2008 Depression and risk for adverse falls in older home health care patients. Res Gerontol Nurs 1: 245-251.
56. Eggermont LH, Penninx BW, Jones RN, Leveille SG, 2012 Depressive symptoms, chronic pain, and falls in older community-dwelling adults: the MOBILIZE Boston Study. J Am Geriatr Soc 60: 230-237.
57. Darowski A, Chambers SA, Chambers DJ, 2009 Antidepressants and falls in the elderly. Drugs Aging 26: 381-394.
58. Van den Berg M, Verdijk NA, Leusink GL, et al, 2011 Depression after low-energy fracture in older women predicts future falls: a prospective observational study. BMC Geriatr 7;11:73.
59. Iaboni A, Flint AJ, 2013 The Complex Interplay of Depression and Falls in Older Adults: A Clinical Review. Am J Geriatr Psychiatry 21: 484-492.
60. Whitson HE, Sanders L, Pieper CF, et al, 2008 Depressive symptomatology and fracture risk in community-dwelling older men and women. Aging Clin Exp Res 20: 585-592.
61. Whooley MA, Kip KE, Cauley JA, Ensrud KE, Nevitt

MC, Browner WS, 1999 Depression, falls, and risk of fracture in older women. Study of Osteoporotic Fractures Research Group. Arch Intern Med 159: 484-490.
62. Søgaard AJ, Joakimsen RM, Tverdal A, Fønnebø V, Magnus JH, Berntsen GK, 2005 Long-term mental distress, bone mineral density and non-vertebral fractures. The Tromso Study. Osteoporos Int. 16:887–897.
63. Forsén L, Meyer HE, Søgaard AJ, Naess S, Schei B, Edna TH, 1999 Mental distress and risk of hip fracture. Do broken hearts lead to broken bones? J Epidemiol Community Health 53: 343-347.
64. Piscitelli P, Metozzi A, Benvenuti E, et al, 2012 Connections between the outcomes of osteoporotic hip fractures and depression, delirium or dementia in elderly patients: rationale and preliminary data from the CODE study. Clin Cases Miner Bone Metab 9: 40-44.
65. Diem SJ, Blackwell TL, Stone KL, et al, 2007 Study of Osteoporotic Fractures. Depressive symptoms and rates of bone loss at the hip in older women. J Am Geriatr Soc 55: 824-831.
66. Diem SJ, Blackwell TL, Stone KL, et al, 2007 Use of antidepressants and rates of hip bone loss in older women: the study of osteoporotic fractures. Arch Intern Med 167: 1240-1245.
67. Herbert C, McKean M, Dantz B, 2010 Osteoporosis in depression: Which patients are at risk? Chronic pain perspectives. 9(4)9-12, 25.
68. Rizzoli R, Cooper C, Reginster JY, et al, 2012 Antidepressant medications and osteoporosis. Bone 51: 606-613.
69. Wu Q, Bencaz AF, Hentz JG, Crowell MD, 2012 Selective serotonin reuptake inhibitor treatment and risk of fractures: ameta-analysis of cohort and case–control studies Osteoporos Int 23: 365-375.
70. Bab I, Yirmiya R, 2010 Depression, Selective Serotonin Reuptake Inhibitors, and Osteoporosis. Curr Osteoporos Rep 8: 185–191.
71. Warden SJ, Hassett SM, Bond JL, et al, 2010 Psychotropic drugs have contrasting skeletal effects that are independent of their effects on physical activity levels. Bone 46: 985-992.
72. Ilias I, Alesci S, Gold P, Chrousos G, 2006 depression and osteoporosis in men: association or casual link? Hormones (Athens) 5: 9-16.
73. Whooley MA, Cauley JA, Zmuda JM, Haney EM, Glynn NW, 2004 Depressive symptoms and bone mineral density in older men. J Geriatr Psychiatry Neurol 17: 88-92.
74. Mussolino ME, Jonas BS, Looker AC, 2004 Depression and bone mineral density in young adults: results from NHANES III. Psychosom Med 66: 533-537.
75. Oh SM, Kim HC, Ahn SV, Rhee Y, Suh I, 2012 Association between depression and bone mineral density in community-dwelling older men and women in Korea. Maturitas 71: 142-146.
76. Laudisio A, Marzetti E, Cocchi A, Bernabei R, Zuccalà G, 2008 Association of depressive symptoms with bone mineral density in older men: a population-based study. Int J Geriatr Psychiatry 23: 1119-1126.
77. Kotsalou I, Valsamaki P, Chatzipetrou A, Fountos G, Adraktas A, Gerali S, 2011 Is major depression in middle-aged men correlated with bone density decrease? A study on Greek population. Hell J Nucl Med 14: 331-336.
78. Hidaka BH. 2012 Depression as a disease of modernity: explanations for increasing prevalence. J Affect Disord 140: 205-214.
79. Mamplekou E, Bountziouka V, Psaltopoulou T, et al, 2010 Urban environment, physical inactivity and unhealthy dietary habits correlate to depression among elderly living in eastern Mediterranean islands: the MEDIS (MEDiterranean ISlands Elderly) study. J Nutr Health Aging 14: 449-455.
80. Ischaki E, Gratziou C, 2009 Smoking and depression: Is smoking cessation effective? Ther Adv Respir Dis 3: 31-38.
81. Palfai TP, Cheng DM, Samet JH, Kraemer KL, Roberts MS, Saitz R, 2007 Depressive symptoms and subsequent alcohol use and problems: a prospective study of medical inpatients with unhealthy alcohol use. J Stud Alcohol Drugs 68: 673-680.
82. Uguz F, Sahingoz M, Gezginc K, Ayhan MG, 2011 Quality of life in postmenopausal women: the impact of depressive and anxiety disorders.Int J Psychiatry Med 41: 281-292.
83. Koster JB, Kühbauch BA, 2011 Vitamin D deficiency and psychiatric patients. Tijdschr Psychiatr 53: 561-565.
84. Takeda S, 2009 Osteoporosis: a neuroskeletal disease? Int J Biochem Cell Biol 41: 455-459.
85. Mezuk B, Eaton WW, Golden SH, 2008 Depression and osteoporosis: epidemiology and potential mediating pathways. Osteoporos Int 19:1-12.
86. Licinio J, Wong ML, 1999 The role of inflammatory mediators in the biology of major depression: central nervous system cytokines modulate the biological substrate of depressive symptoms, regulate stress-responsive systems, and contribute to neurotoxicity and neuroprotection. Mol Psychiatry 4: 317-327.
87. Rush AJ, Schlesser MA, Orsulak PJ, et al, 1997 Dexamethasone response, thyrotropin-releasing hormone stimulation, rapid eye movement latency, and subtypes of depression. Biol Psychiatry 41: 915-928.
88. Rush AJ, Giles DE, Schlesser MA et al, 1996 The dexamethasone suppression test in patients with mood disorders. J Clin Psychiatry 57: 470-484.
89. Cizza G, Ronsaville DS, Kleitz H, et al, 2012 Clinical subtypes of depression are associated with specific metabolic parameters and circadian endocrine profiles in women: the power study. PLoS One, 7:e28912.
90. Warden SJ, Robling AG, Haney EM, Turner CH, Bliziotes MM, 2010 The emerging role of serotonin (5-hydroxytryptamine) in the skeleton and its mediation of the skeletal effects of low-density lipoprotein receptor-related protein 5 (LRP5). Bone 46: 4-12.
91. Bliziotes M, 2010 Update in Serotonin and Bone. J

Clin Endocrinol Metab 95: 4124–4132.
92. Karsenty G, Ferron M, 2012 The contribution of bone to whole-organism physiology. Nature 18: 481: 314-320.
93. Yirmiya R, Goshen I, Bajayo A, et al, 2006 Depression induces bone loss through stimulation of the sympathetic nervous system. PNAS 103: 16876–16881.
94. Ducy P, Karsenty G, 2010 The two faces of serotonin in bone biology. J Cell Biol 191(1):7-13.
95. Baron R, Hesse E, 2012 Update on bone anabolics in osteoporosis treatment: rationale, current status, and perspectives. J Clin Endocrinol Metab 97: 311-325.
96. Krishnan V, Bryant HU, Macdougald OA, 2006 Regulation of bone mass by Wnt signaling. J Clin Invest 116: 1202-1209.
97. van Dijk SC, de Herder WW, Kwekkeboom DJ, et al, 2012 5-HIAA excretion is not associated with bone metabolism in carcinoid syndrome patients. Bone 50: 1260-1265.
98. Yadav V, Oury F, Suda N, et al, 2009 Leptin regulation of bone mass, appetite and energy expenditure relies on its ability to inhibit serotonin synthesis in the brainstem. Cell. 138: 976-989.
99. Gimble JM, 2011 Leptin's Balancing Act Between Bone and Fat. JBMR 26: 1694-1697.
100. Cizza G, Nguyen VT, Eskandari F, et al, 2010 Low 24-hour adiponectin and high nocturnal leptin concentrations in a case-control study of community-dwelling premenopausal women with major depressive disorder: the Premenopausal, Osteopenia/Osteoporosis, Women, Alendronate, Depression (POWER) study. J Clin Psychiatry 71: 1079-1087.
101. Kahl KG, Greggersen W, Rudolf S, et al, 2006 Bone mineral density, bone turnover, and osteoprotegerin in depressed women with and without borderline personality disorder. Psychosom Med 68: 669-674.
102. Pérez-López FR, 2007 Vitamin D and its implications for musculoskeletal health in women: an update. Maturitas 58: 117-137.
103. Lee DM, Tajar A, O'Neill TW, et al, 2011 Lower vitamin D levels are associated with depression among community-dwelling European men. J Psychopharmacol 25: 1320-1328.
104. Jorde R, Sneve M, Figenschau Y, Svartberg J, Waterloo K, 2008 Effects of vitamin D supplementation on symptoms of depression in overweight and obese subjects: randomized double blind trial. J Intern Med 264: 599-609.
105. Zhao G, Ford ES, Li C, Balluz LS, 2010 No associations between serum concentrations of 25-hydroxyvitamin D and parathyroid hormone and depression among US adults. Br J Nutr 104: 1696-1702
106. Walker MD, Rubin M, Silverberg SJ. 2013 Nontraditional manifestations of primary hyperparathyroidism J Clin Densitom 16: 40-47.
107. Dobolyi A, Dimitrov E, Palkovits M, Usdin TB, 2012 The neuroendocrine functions of the parathyroid hormone 2 receptor. Front Endocrinol (Lausanne). 2012;3:121.
108. Herrán A, Amado JA, García-Unzueta MT, Vázquez-Barquero JL, Perera L, González-Macías J, 2000 Increased bone remodeling in first-episode major depressive disorder. Psychosom Med 62: 779-782.
109. Haney EM, Warden SJ, Bliziotes MM, 2010 Effects of selective serotonin reuptake inhibitors on bone health in adults: time for recommendations about screening, prevention and management? Bone 46: 13-17.