Opinion

Depression as a risk factor for osteoporosis

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Osteoporosis is a major public health threat. Multiple studies have reported an association between depression and low bone mineral density, but a causal link between these two conditions is disputed. Here we review the endocrine and immune alterations secondary to depression that might affect bone mass. We also discuss the possible role of poor lifestyle in the etiology of osteoporosis in subjects with depression and the potential effect of antidepressants on bone loss. We propose that depression induces bone loss and osteoporotic fractures, primarily via specific immune and endocrine mechanisms, while poor lifestyle habits and use of specific antidepressants are potential contributory factors.

Unrecognized link between depression and osteoporosis

Osteoporosis is a public health threat. In 2005, more than 2 million fractures occurred in the United States, 70% of which occurred in women, with a healthcare system financial strain of 17 billion dollars [1]. This burden is predicted to increase, and by 2020, it is anticipated that 14 million women and men will be affected by osteoporosis in the US, with a projected 50% increase in fractures at a cost of 25 billion dollars per year [1].

Recognized risk factors for osteoporosis include menopause, Caucasian or Asian race, a thin frame, physical inactivity, smoking, alcohol use, inadequate calcium and vitamin D intake, corticosteroid use, and certain medical conditions. We suggest that depression is another risk factor for osteoporosis. Major depressive disorder (MDD) is an important cause of disability in the US and one of the leading causes of disability worldwide [2]. Despite a large body of evidence, however, depression is not listed among the risk factors for osteoporosis [3]. We suggest a causal link between MDD and osteoporosis, analyze the clinical consequences of this relationship, and propose potential mechanisms.

Relationship between depression, bone mass, and osteoporotic fractures

In 1994, Schweiger *et al.* reported a 15% deficit in spine bone mass measured by computed tomography (CT) in patients with major depression, spurring a growing number of reports investigating a potential relationship between depression and osteoporosis. Many of these relevant reports were described in detail in our previous review article [4] and representative studies are listed in Table 1.

Determining whether decreased bone mass in subjects with depression translates into increased fracture risk is crucial. Bone mineral density (BMD) is considered a reliable predictor for fractures and accounts for approximately 70% of the risk variability [5]. The remaining 30% might depend on factors like biomechanical bone strength and anatomical properties not captured by conventional methods (e.g. dual-energy X-ray absorptiometry (DXA) measurements) [6]. In a large study of patients with hip fractures, approximately half of the subjects were not osteoporotic at the hip [7] confirming that, in addition to BMD, other factors contribute to fracture risk. Because of the need for a large sample and long follow-up, few studies have examined osteoporotic fracture prevalence in subjects with depression.

In the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, postmenopausal women with vertebral fractures reported more depressive symptoms than women without vertebral fractures [8], but it remained unclear whether depression was reactive to fractures or causative. In a prospective study of older Mexican-American women, higher levels of depression predicted self-reported fractures [9]. In a prospective, population-based study of women aged 50 or older conducted in Norway, women with the highest level of distress, defined as depression associated with life dissatisfaction, nervousness, loneliness, sleep disorders, and uneasy feelings, were at greater risk for hip fracture [10]. Likewise, in a large cohort of subjects aged 25 through 74 (the NHANES I study), and followed for 22 years, depression predicted hip fractures, a finding that remained significant after adjustment for age, gender, race, body mass index (BMI), smoking, alcohol, and physical activity [11]. Interestingly, no significant differences were found in spine or femur BMD between depressed women and controls. Middle-aged women with depression had a 40% increase in risk for non-vertebral fractures compared to women without depression [12]. This association remained strong in women with depression after adjustment for their increased propensity for falls. In summary, a large body of evidence supports a causal link between MDD and osteoporosis and osteoporotic fractures, a possibility that should be investigated further at several bone sites of high fracture incidence, and not only at the hip.

Possible causative factors for bone mass deficit in subjects with depression

The theoretical framework in Figure 1 depicts the synergistic action of endocrine and immune alterations

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Table 1. Representative studies of bone mineral density in subjects with depression[a]

Study design setting	Diagnosis, gender, sample size	Age (Menopausal State)	Main findings
Cross-sectional study at a psychiatric clinic (Petronijevic *et al.* 2008; Ref. [18])	Women with unipolar depression (N=73) Control women matched by age and osteoporosis risk factors (N=47)	4th decade (All premenopausal)	Women with depression had: ⇓BMD at the spine and femoral neck Approximately 45% had osteoporosis Duration of depression was inversely related to BMD
Cross- Sectional Evaluation of a Prospective Cohort: The POWER Study (Eskandari *et al.* 2007; Ref. [16])	Women with current or past MDD (N=89) Control women (N=44) matched by age, BMI, race	3rd decade (All premenopausal)	Women with depression had: ⇓BMD at the spine and femoral neck, ⇑ Prevalence of low BMD at the at the femoral neck and total hip ⇑Pro-inflammatory and ⇓ anti-inflammatory cytokines
Cross-Sectional Evaluation of a Prospective Cohort (Niti *et al.* 2007; Ref. [52])	Healthy subjects Community sample (N=2,611; men=963, women=1648)	5th decade (All women postmenopausal)	⇑ Risk of having osteoporosis if depressed (OR, 2.32; 95% CI, 1.13–4.76)
Prospective evaluation of a Mexican American cohort (Tolea *et al.* 2007; Ref. [9])	Women with depressive symptoms (N=1,350)	7th decade	High depressive symptomatology was predictive of self-reported osteoporosis (OR, 1.42; 95% CI, 1.05–1.92) Self-reported fractures (OR, 1.43; 95% CI, 1.03–1.99)
Consecutive series of outpatients at a psychiatric clinic (Kahl *et al.* 2006; Ref. [13])	Women with borderline personality disorder (BPD) (N=38; 16 w/o MDD; 22 with MDD)	2nd–3rd decades (All premenopausal)	⇓ BMD (Z scores) in subjects with BPD+MDD at the lumbar spine (versus subjects with BPD only) lumbar spine and forearm versus historical controls (normative data)
Prospective cohort study: the NHANES I Study (Mussolino, 2005; Ref. [11])	Healthy subjects White and black men and women (N=6,195)	25–74 yr at baseline (Pre and/or postmenaopausal women)	Depression was predictive of hip fracture (Hazard Ratio, 1.9; CI, 1.1.3–3.21; P=0.01)
Cross-sectional evaluation of a large cohort (Wong *et al.* 2005; Ref. [42])	Healthy subjects; stratified sample of community living Chinese men (N=1999)	65 yr or older (mean 72 yr)	Adjusted hip BMD was 2.1% lower in men with depression (RR, 1.4; CI 1–2.08; P= 0.05) AP spine was not different between groups No differences in fracture rates between groups 8.5% of men met criteria for clinical depression.
Cross-sectional study of a national probability sample: NHANES III Study (Mussolino *et al.* 2004; Ref. [40])	Healthy subjects Civilian non institutionalized US population from 1988 to 1994 non-Hispanic White, non-Hispanic Black and Mexican-American men (N=2,528) and women (N=2,643)	20 – 39 yr	No differences in BMD in women Men with MDD had 5.1% lower BMD than men w/o MDD; Risk-adjusted ORs for men were: MDD, 1.65 (CI 1.08–2.52, P=0.05); dysthymia, 1.84 (CI 1.29–2.62, P=0.01)
Prospective cohort study of risk factors of osteoporosis (Whooley *et al.* 2004; Ref. [41])	Healthy subjects (N=523) evaluated at baseline and a random subset evaluated 3.6 yr later	50 yr and above	No association between depressive symptoms and BMD No differences in BMD in subjects with 6 or more depressive symptoms vs subjects with 5 or fewer symptoms
Prospective population-based cohort: Cardiovascular Health Study (Robbins *et al.* 2001; Ref. [46])	Healthy subjects Caucasian and African-American men and women (N=1552)	65–100 yr (All women postmenopausal)	Depression was negatively associated with total hip BMD in the full cohort, and among Caucasians and African-Americans After statistical adjustment, depression accounted for 2% of the total hip BMD variability

[a]AP, anterior–posterior; BMD, bone mineral density; CI, confidence interval; MDD, major depressive disorder; OR, odds ratio.

underlying altered BMD and increased bone fragility in subjects with MDD.

Hypothalamo–pituitary–adrenal (HPA) axis and the role of cortisol

Hypercortisolemia is considered an important causative factor for bone deficits in depression. Depression causes a sustained and protracted activation of the stress system, stimulating the release of hypothalamic corticotropin-releasing hormone (CRH) neuron via circuits connecting the prefrontal cortex, the hippocampus, the amygdala, and the hypothalamus, and thereby increasing cortisol secretion. It is of note that the increased levels of cortisol in plasma, or of urinary free cortisol (UFC), are usually much less pronounced in depression than in Cushing syndrome. However, cortisol has been measured only in a small number of studies focused on depression and osteoporosis. These studies documented either increased plasma cortisol [13,14] or increased UFC [15], though no differences were found in other studies [13,16–20]. Mild alterations of the HPA axis in depression become more apparent under stress. For example, salivary cortisol

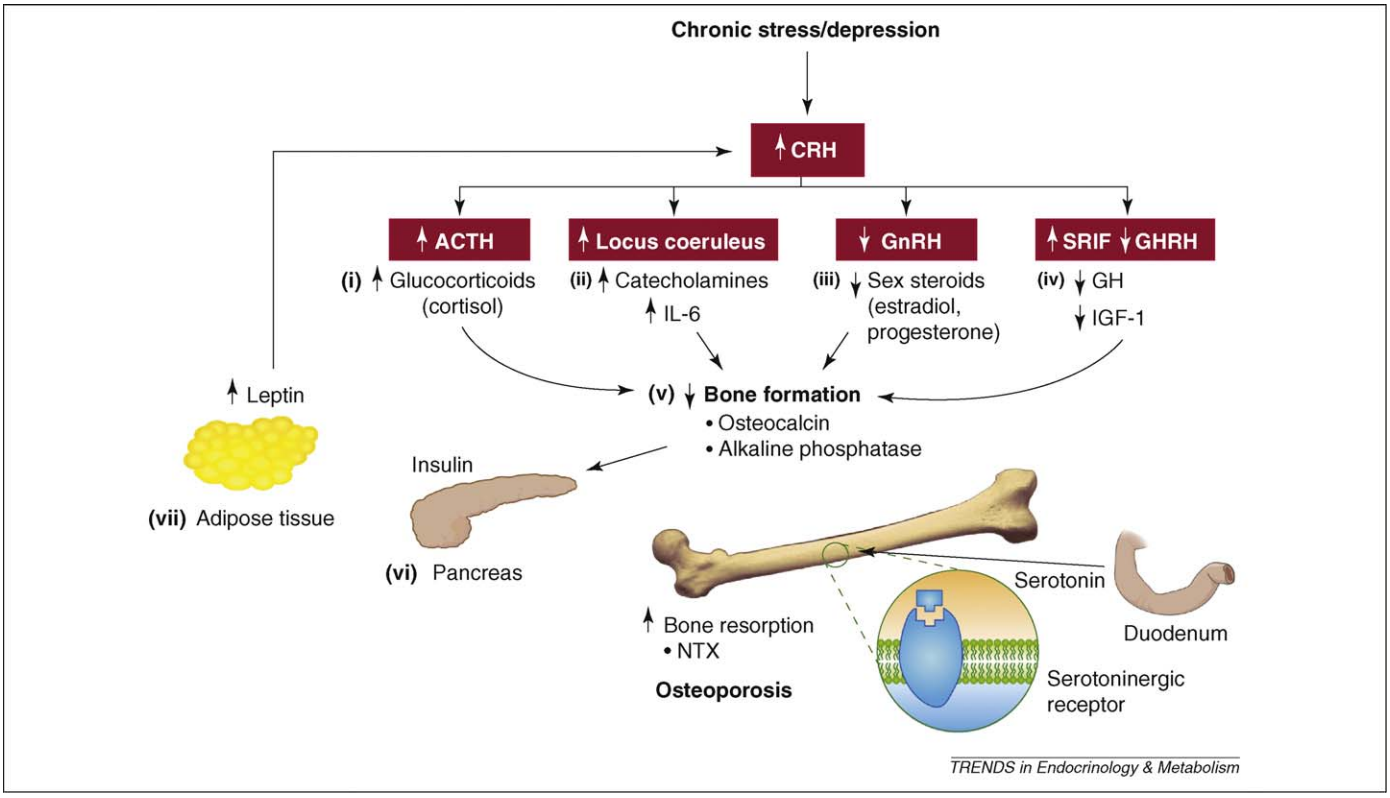

Figure 1. Potential mechanisms of bone loss in depression. The model implicating hypercortisolemia **(i)** as a major cause of osteoporosis is derived from the well-known effect of increased cortisol in subjects with Cushing syndrome. The other main effector branch of the stress system, the sympathetic system **(ii)**, modulates the production of pro-inflammatory cytokines, including interleukin 6 (IL-6), a potent bone resorption agent. As evolutionarily appropriate in chronic stress situations including depression, the processes for reproduction and growth become inhibited, resulting in decreased levels of estrogens **(iii)** and growth hormone (GH)/insulin-like growth factor type 1 (IGF-1) **(iv)**. Taken together, the combination of increased cortisol, IL-6, decreased sex steroids and GH leads to reduced bone mass as the net result of decreased bone formation and increased bone resorption according to the markers of bone turnover. Physiological amounts of osteocalcin regulate **(vi)** insulin expression in the pancreas and adiponectin in **(vii)** adipose tissue. The complex endocrine and immune imbalances depicted in this figure predispose subjects with depression to other serious medical consequences such as central obesity, altered insulin sensitivity, subclinical inflammation, and increased cardiovascular morbidity and mortality. CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropic hormone; GnRH, gonadotropin releasing hormone; NTX, N-telopeptides.

following a public speech task was higher in 9 depressed postmenopausal women compared to 10 non-depressed postmenopausal women [21]. Depressed women also had significantly lower total lumbar and right femur BMD, demonstrating a negative relationship between post-stress salivary cortisol and BMD. In most of these studies, subjects with depression were treated pharmacologically. Therefore, variable cortisol values in these studies might be due to normalization of hypercortisolemia secondary to drug treatment and clinical improvement. In addition, circadian variation and the fact that cortisol levels are sensitive to venipuncture could contribute to the variability in these findings. In summary, alterations of the HPA axis are established features in patients with depression, but they may or may not be evident depending on the severity of depression and on the specific parameters of the HPA axis that are measured.

Sympathetic system

Whereas the importance of the HPA axis in the pathogenesis of bone loss secondary to depression has been recognized for a long time, Yirmiya *et al.* recently shifted focus to the role of the other efferent limb of the stress system, the catecholaminergic axis. Stress causes bone loss in rodents via increased activity of this axis [22]. Two-week exposure of mice to various severe stressors resulted in bone loss that was preventable by antidepressants. Further, bone loss was mediated by increased activity of the catecholaminergic system because it could be partially ameliorated by β-blockers [22].

The POWER study did not detect differences in urine epinephrine, norepinephrine, or dopamine levels (as obtained from 24 h urine collection) between depressed women and controls [16]. It is however possible that measurements of urinary catecholamines might not be sufficiently sensitive to detect changes in the sympathetic system secondary to mood alterations [23]. Very recently, the population-based First Israeli National Health Interview Survey reported a strong association between generalized anxiety disorders (GAD) (independent of major depression) and osteoporosis [24]. Interestingly, the prevalence of fractures was lower in subjects on β-blockers [25], implying that increased activity of the sympathetic–adrenal system might play a role in osteoporosis.

We advocate more clinical research in this area, especially in post-traumatic stress disorder (PTSD) and other conditions characterized by alterations of the sympathetic nervous system.

Leptin

Leptin causes bone loss in rodents by centrally inhibiting bone formation via activation of the sympathetic system

[26]. Reports of serum leptin levels in depressed subjects are conflicting, with studies finding either no differences [13,27], lower levels in depressed men [28], elevated levels in depressed men and women [29], or elevated levels only in depressed women [30]. These studies might be conflicting because in observational investigations it is difficult to disentangle the direct effects of mechanical stimulation (increased body weight) on the osteoblast versus the effect of a fat product (i.e. leptin) on the neuroendocrine bone axis. It is also possible that the involvement of leptin in bone loss is influenced by mechanical stimulation. For example, load exercise directly stimulates the osteoblast. One can assume then that heavier people, who presumably have increased fat mass, tend to have stronger bones. A negative effect of leptin on bone mass would still be compatible with higher body weight being stimulatory to bone. Because leptin has a wide normal range, two individuals with the same fat mass may have very different leptin levels [31]. From these studies it is apparent that further research on the correlation between the leptin axis and depression is needed.

Immune factors: the role of cytokines

Depression is associated with immune dysregulation characterized by increased cytokine activity, specifically of interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) [32]. Cytokines are potent stimulators of the HPA axis and might contribute to hypercortisolism in depression. However, only a few studies have addressed this question. We found a profound dysregulation of plasma cytokines, measured hourly for 24 h (from 8 am until 8 am the next day) [16]. Levels of pro-inflammatory cytokines IL-1β, IL-2, IL-6 and TNFα were significantly increased in premenopausal women in remission from depressive symptoms compared to age/BMI/ethnicity-matched healthy controls, whereas anti-inflammatory IL-10 values were lower and levels of anti-inflammatory IL-13 were similar between the two groups [16]. Increased levels of TNF-α and IL-6 [13], with no differences in TNF-α receptors, have also been reported [27]. To study immune alterations non-invasively, we developed a method to quantify cytokines in sweat. Cytokine levels in sweat correlated closely with plasma levels, making this non-invasive approach potentially applicable to large-scale studies [33]. Increased levels of oxidative stress might represent another potential pathway to both depression and osteoporosis [34]. More research is needed in this promising area.

Vitamin D and parathyroid hormone (PTH)

Several studies reported an association between vitamin D and PTH in depression [13,14,16–20,27,35]. We found that women with depression had slightly higher PTH, and had lower 25-OH vitamin D and ionized calcium levels compared to controls [16]. Interestingly, low vitamin D levels might play a role in seasonal affective disorder (SAD), a clinical variant of depression that worsens in the Northern hemisphere during winter, because SAD improves with vitamin D supplementation, sun exposure and light therapy. Vitamin D receptors are present in several human brain areas involved in neuroendocrine and autonomic functions including the hypothalamus, the nucleus basalis of Meynert and the substantia nigra [36], potentially supporting a direct role of vitamin D in modulating mood and behavior in depression.

Gender effects

Little attention has been paid to the role of estrogens in osteoporosis-related depression. No major differences were evident in age at menarche [14,16,18,19,37], number of pregnancies [14,16,18], oral estrogen use [38,39], or irregular menses [17] between subjects with depression versus controls.

Another unanswered research question concerns whether there is a different susceptibility in women versus men to fractures associated with depression. Bone mass is generally lower in men with depression compared to non-depressed men, especially at the total femur [30,40–42]. Men tend to have fractures at higher BMD values than women [43]. In a longitudinal cohort study conducted in Norway, both pre- and post-menopausal women with mental distress (defined as depression insomnia and coping problems) had increased fracture risk, but this association was not found in men [44]. Use of antidepressants such as fluoxetine has been associated with low testosterone levels in older men and increased prolactin in both genders. Conversely, testosterone supplementation in men seems to improve some of the symptoms of depression.

There is a strong need for rigorous studies on the effects of antidepressants on testosterone levels and the potential repercussions on bone mass. Women commonly experience periodic disruptions of the ovarian cycle during their reproductive years that translate into transient hypoestrogenemia. These episodes are often triggered by increased stress and anxiety. More research is needed to examine the contribution of alterations of the menstrual cycle on depression-induced osteoporosis in women. Physicians should encourage women with depression to maintain a monthly record of their menstrual cycle. A potential interaction between sex hormones and skeletal sites also requires further investigation.

Lifestyle factors and osteoporosis

The association between depression and osteoporosis might be mediated or perpetuated by an unhealthy lifestyle. This question generally has been addressed in a retrospective fashion and often in a self-reported form. Such studies report no differences in dietary calcium intake [16,37–40] or calcium supplementation [12,35] in subjects with depression compared with controls. Smoking has been correlated with bone loss [3], but only a few studies reported that depressed subjects contained a higher proportion of smokers [11,12,40] and most studies found no differences between the groups [8,16–18,38,39,41,45–47]. Weight-bearing physical activity helps to maintain bone mass and, in general, subjects with depression were less active than controls [12,38,41,42,46,48,49], but some studies observed no differences in physical activity [11,16,35,40]. Low BMI is a well-known risk factor for osteoporosis and fractures [50]. In lean elderly women with depressive symptoms, life-long exercise was protective against falls and fractures [48]. Alcohol intake is also an established risk factor for

osteoporosis [3] and yet was found to be either similar in subjects with depression and controls [16,40–42,51,52] or significantly lower in subjects with depression [11,12,46]. Therefore this factor is unlikely to play a role in determining low bone mass in subjects with depression. Sleep disturbances and sleep deprivation are often observed in MDD and are known to increase cortisol and raise levels of pro-inflammatory cytokines [53], suggesting an additional link between depression and osteoporosis. Based on the limited evidence available, we suggest that lifestyle factors play a relatively small role in inducing bone loss in subjects with depression.

Effect of antidepressants on bone mass and osteoporotic fractures

Low bone mass in medicated psychiatric patients has been reported since the 1990s [4]. In a large cohort, elderly women treated with selective serotonin reuptake inhibitors (SSRIs) experienced greater bone loss at the hip; this was a class-specific effect because no increase was observed in patients treated with tricyclic antidepressants (TCAs) [39]. Serotonin transporter receptors have been identified on osteoblasts [54], making a direct effect on bone mass biologically plausible. Antidepressant use, however, was not associated with lower bone mass in two small studies [16,18]; on the other hand, a third study reported greater bone resorption in a similar sample of patients taking SSRIs [17]. Because of the limited statistical power in small studies, these findings should be taken with caution.

Use of SSRIs and TCAs might induce fractures by increasing the risk of falls, especially in the elderly, possibly through cardiac arrhythmias or postural hypotension [55]. Two large studies in elderly subjects reported that subjects on SSRIs, secondary amine TCAs, or tertiary amine TCAs were at increased risk of hip fracture [56,57]. Use of SSRIs was associated with a 2.25-fold increase in fracture risk in a large cohort study conducted in Rotterdam [58]. In fact, this study identified a clear relationship between treatment duration and increased risk, detectable as early as 6 weeks after commencement of medication. The Women's Health Initiative Observational Study [59] reported that, in 80,000 women aged 50 to 79 years, antidepressant use was associated with more fractures at the spine and other sites, and even in the absence of changes in BMD.

As a large case-control Danish study has revealed [60], antidepressants may differ in their associated fracture risk. Most SSRIs were associated with a dose-dependent increase in fracture risk. TCAs with sedating effects (e.g. amitriptyline and clomipramine) were associated with fractures, whereas imipramine and nortriptyline were not. Other antidepressants such as mianserin and mirtazapine carried no increased risk of fractures in this population.

Depression, other co-morbid psychiatric conditions, and osteoporosis

MDD is often observed in association with anxiety and other mood disorders, but it is unclear whether psychiatric co-morbidity aggravates bone loss. Anxiety was associated with lower hip BMD in adolescent girls [45]. In addition, BMD at the lumbar spine was lower in women with depression and borderline personality disorder compared to women with depression only [13]. Girls suffering from anorexia nervosa and depression were also reported to have lower BMD than girls with anorexia nervosa only [37]. Men, but not women, with depression and dysthymia, a chronic form of a depression disorder that is not as severe as MDD, had lower BMD at the level of the hip compared to men with depression only [40].

Conclusions

MDD is a risk factor for low BMD and fractures. This has been shown in middle-aged women, elderly subjects of both genders, White, African-Americans and Mexican-Americans, and for both vertebral and non-vertebral sites. A variety of mechanisms have been proposed to explain this association, but lifestyle factors and the use of a particular class of anti-depressants appear to play only contributory roles. Irrespective of the specific cause(s), subjects with depression should be considered for osteoporosis screening and, conversely, subjects with decreased BMD should be considered for screening for depression. Adequately powered, well-adjusted, longitudinal, controlled studies of bone

Box 1. Outstanding research questions

The overarching research goal is to further characterize the pathogenesis of osteoporosis in subjects with depression in the general context of the medical consequences of depression. Listed below are some of the most important questions that should be prospectively tested.

- The rate of developing bone deficit in depression should be established.
  - Is peak bone mass ever fully achieved in subjects with depression?
  - Are there critical life periods in which the skeleton is more susceptible to bone loss?
  - The perimenopausal period, with its declining estrogen levels and concomitant mood changes, is a primary target for further studies.
  - Despite requiring long follow-up, the incidence of fractures in women with depression should be prospectively evaluated.
- The reversibility of bone loss, secondary to therapeutic interventions or spontaneous clinical resolution, should be explored.
- Further clinical evidence is needed to establish conclusively the potential side effects of SSRIs on bone mass in subjects with depression.
- Studies are needed to determine whether the association between depression and BMD is entirely mediated by the endocrine and immune alterations described here, and whether this association is more likely to be evident during active disease (state), or whether it is also associated with the condition of depression *per se* (trait) via some, as yet unclear, genetic mechanisms.
- Studies are needed to determine how genetic background might modulate the association between depression and fracture risk.
- More research is warranted in men and women with anxiety disorders, especially PTSDs, in men suffering from depression, and in girls with depression and anxiety.
- The relationship between sleep disturbances and bone loss, as well as fractures secondary to falls, should be studied in sleep-deprived subjects with mood disorders.
- Given the current epidemic of obesity and the increasing use of bariatric surgery, the interaction between depression, weight loss, and bone loss should be studied in post-obese subjects with mood disorders.

turnover also are warranted in subjects with depression. A summary of outstanding research questions is presented in Box 1.

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