

Review**Depression and Osteoporosis in Men: Association or Casual Link?**Ioannis Ilias,¹ Salvatore Alesci,² Philip W. Gold,² George P. Chrousos³

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ABSTRACT

The longer life expectancy of women than that of men and, therefore, the longer exposure to fracture risk has, at least partially, led to neglect of osteoporosis in men. Recently, unipolar depression, which is 2 times more frequent in women than in men, has been linked to osteoporosis. However, it is quite possible that this diagnosis may escape detection in men because of a different behavioral phenotype between the genders. A potential mechanism of bone loss in depression has been proposed, involving concurrent activation of the hypothalamo-pituitary-adrenal and sympatho-adrenal axes, suppression of the gonadal and somatotrophic axes, and high interleukin-6 and low leptin levels. We suggest that similar neurohormonal changes may cause osteoporosis in men.

Key words: Depression, Male, Osteoporosis

OSTEOPOROSIS IN MEN

Over the last two decades, osteoporosis has received increasing attention as a major health problem worldwide. It has been estimated that in the United States alone, 10 million people suffer from osteoporosis, and 18 million more are afflicted with osteopenia, which has been associated with an increased risk for nontraumatic fractures later in life.¹ Osteoporosis is still regarded mainly as a women's disease. This could be attributed to a higher bone mass in men and the absence of menopause, as well as to the fact that men undergo fewer bone mineral

density (BMD) measurements than women.² Since life expectancy has considerably increased worldwide over the last century (with men's longevity, however, still lagging somewhat behind that of women: 75v. 80 years in the U.S.), more and more older men are now expected to develop multiple coexisting illnesses contributing to bone loss. With advancing age, the likelihood of accidental falls also increases and this is accompanied by an elevated likelihood of sustaining fractures. In the following review we examine the tentative association of depression and osteoporosis in men.

Epidemiology of low bone mineral density in men

Investigators have used data from the Third National Health and Nutrition Survey (NHANES III) to estimate the prevalence of low BMD in the United States.³ Specifically, they applied the World

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Health Organization (WHO) criteria to define osteopenia ($-2.5 \text{ SD} \leq \text{BMD t-score} \leq -1 \text{ SD}$) and osteoporosis ($\text{BMD t-score} < -2.5 \text{ SD}$) and used two different cutoffs for men, based either on young normal male or female reference groups aged 20-29 years. With male cutoffs, 28% to 47% (9 to 13 million) of men aged 50+ years were estimated to have osteopenia and 3% to 6% of men (1 to 2 million) osteoporosis. Using female cutoffs, 15 to 33% (5 to 11 million) had osteopenia and 1 to 4% (0.3 to 1 million) had osteoporosis.

Epidemiology of osteoporotic fractures in men

It is a common assumption that women sustain more fractures than men. However, the relation between BMD and fractures is similar in men and women,⁴ and cumulative cross-sectional data on fracture incidence at all ages, all sites and all activities have shown that men are more likely to incur fractures than women.⁵ The most common osteoporotic fractures are those of the hip and vertebral bodies, followed by those of the forearm, humerus, tibia, iliac bones and the ribs. Of the 1.7 million hip fractures that occurred worldwide in 1990, 28% were in men and, according to a projection that takes into account the increasing longevity of men, out of 4 million hip fractures expected in 2025, 1.2 million will occur in men.⁶ The lifetime risk of hip fracture in men has been estimated at 6%.⁷ Hip fractures account for the greatest morbidity and mortality among fractures, which are higher in men than women for reasons that remain unclear.⁸ Up to 50% of men need to be hospitalized after a hip fracture and up to 80% of those who survive are unable to regain their normal level of functional independence.⁹ Moreover, men have a two-fold greater likelihood of dying in hospital after a hip fracture compared to women.¹⁰ In men aged 60 to 69 years, the decrease in life expectancy after a hip fracture is 11.5 years.⁸ The incidence of vertebral fractures is probably underestimated, as not all patients may seek medical attention because of the nonspecificity of the symptoms associated with such fractures, such as low back-pain, height loss and kyphosis (usually revealed by radiological screening).¹¹

DEPRESSIVE DISORDERS

Depressive disorders affect the person's body, mood and cognition and take different forms, including major (or unipolar) depression, dysthymia and bipolar disorder, as described in the fourth edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR).¹² Major depression must be differentiated from dysthymia, a less severe type of depression involving long-term chronic symptoms that may interfere with the person's social functioning and feeling of well-being, but are not disabling. Bipolar disorder (or manic-depressive disorder) is characterized by cycling mood-swings between euphoria and dysphoria.

Unipolar Depression in men

The WHO estimates that depression is currently the fourth leading cause of worldwide, and predicts that by the year 2020 it will be the second.¹³ As with osteoporosis, women have mostly been the main focus of attention for depression, because the prevalence of this disorder appears to be higher in women than in men. Epidemiological studies have consistently reported that major depression is twice as prevalent in women as in men.¹⁴ Thus, according to the National Comorbidity Survey I, the lifetime prevalence of major depression in men in the United States is 12.7% compared to 21.3% in women, while the female-to-male relative risk is 1.7.¹⁵

Several hypotheses have been put forward to explain the gender difference in the prevalence of unipolar depression. Biological theories have focused on sex-differences in neurotransmitters and neuroendocrine systems^{16,17} as well as on genetic factors.¹⁸ On the other hand, psychosocial theories have pointed to social childhood environment, social roles and cultural norms, economic dependence, vulnerability and coping style.¹⁹ Finally, diagnostic biases, including the tendency of females to more often report depressive symptoms than males together with gender differences in help-seeking behavior and measurement procedures cannot be excluded.²⁰ Another important gender-related difference is that suicide attempts are more common in women, while men more often completed suicides.²¹

It has recently been suggested that the presentation of depressive symptoms may be different in males and females. The Gotland Study has shown that, in addition to the classic symptoms cited by the DSM IV, the male depressive syndrome may include several atypical manifestations, which may lead family/general practitioners and even psychiatrists to mistake depression for diagnoses of comorbid states, such as alcoholism, drug abuse or antisocial personality disorder.²² Further support for this concept comes from the finding that in religious communities that do not permit antisocial behavior or alcohol/drug use, unipolar depression is equally distributed among men and women.^{23,24} To better identify depressed males, the Gotland Male Depression Scale includes, in addition to the typical features of unipolar depression, several atypical manifestations. Educational programs and improvements of psychiatric services on the island of Gotland have been accompanied by a significant decrease in the rate of male suicides.²⁵

DEPRESSION AND OSTEOPOROSIS IN MEN: ASSOCIATION OR CASUAL LINK?

Several studies have examined the association between major depression and low BMD. Most of the studies on depression and osteoporosis have been conducted on postmenopausal women and only a few of them have included depressed premenopausal women or men. Recently, a cross-sectional study evaluated the association between BMD (measured by DEXA) and depression in a population of 1,566 subjects aged 65 or older, randomly selected from the participants of the Cardiovascular Health Study, a longitudinal, long-term follow-up study conducted at the University of Pittsburg and the University of California at Davis Clinical Centers. Of the 16% subjects clinically diagnosed with major depression by means of the Center for Epidemiological Studies 10-item Depression Scale (CES-Dm), 9% had low BMD. Patients with higher CES-Dm scores also registered lower BMD, after adjustments for bone mass index, age, kilocalories of activity, gender, race, smoking and drinking.²⁶

Review of the published studies on osteoporosis and depression in men

In a population of 80 patients with depression (27 men, mean age: 58 years; 53 women, mean age: 62 years), diagnosed according to the DSM III R, the lumbar-spine BMD values measured by quantitative computed tomography (qCT) were approximately 15% lower than in a group of 88 nondepressed subjects (30 men, mean age: 63 years and 58 women, mean age: 58 years).²⁷ Risk factors for bone loss, such as smoking, history of excessive or inadequate levels of exercise, or history of estrogen treatment did not yield any additional effect, suggesting an effect of depression per se on bone loss. A follow-up of this study, carried out on 18 depressed subjects (10 men, 8 women) and 21 age-matched nondepressed controls (14 men, 7 women) from the original cohort, showed that bone loss over 24 months was significantly greater in depressed subjects than in control subjects. Moreover, bone loss in depressed men was 6% greater than in depressed women.²⁸

In a case series of psychiatric inpatients (35 men, mean age: 36 years and 33 women, mean age: 44 years) consecutively hospitalized for depression (diagnosed based on the DSM III R) or other mental conditions, depressed subjects (n=21) had a significantly lower BMD (measured by dual-photon absorptiometry at the hip and spine) than age- and gender-matched controls. Again, bone loss was more severe in depressed men than in depressed women. A negative correlation between plasma cortisol and bone mineral density was observed in depressed subjects of both sexes, while in men there was a positive correlation between BMD and testosterone levels.²⁹

In a recent large cross-sectional study of 2000 oriental men aged 65 to 92 years, 8.5% of the subjects were depressed and depression was associated with a 1.4-fold (95% CI 1.00 to 2.08) relative risk of being diagnosed as having at least osteopenia (assessed by DEXA).³⁰

Limitations of the published studies on osteoporosis and depression in men

The studies summarized here are important because they point to the tentative existence of an as-

sociation between depression and osteoporosis in men. However, it is important to note some of their limitations. Most studies can establish only the existence of an association rather than a causal link between depression and osteoporosis. Different instruments have been used to diagnose and assess the severity of depression. The populations studied were heterogeneous: subjects who were actively depressed were often pooled together with subjects who only carried a history of depression. Retrospective evaluation of history of depression has limited reliability when it is solely based upon subject recollection. Furthermore, the sample size in some studies was small. Another issue that has not been explored is that depressed subjects may spend much time indoors, thus avoiding exposure to sunlight (leading to vitamin D deficiency) or lead sedentary lives.³¹

Endocrine correlates of Depression in men: implications for bone loss

Several endocrine changes have been described in depressed male patients. Some of them may negatively influence bone metabolism,³² as discussed below.

Hypothalamo-pituitary-adrenal (HPA) and sympathoadrenal axes

Neuroendocrine abnormalities are a common finding in depressed patients. The most consistent finding is that depressed subjects have levels of cortisol whose magnitude may sometimes resemble those seen in mild Cushing's disease.³³ In one study, the 24-h profile of plasma cortisol and corticotropin (ACTH) was determined in 18 men suffering from major depressive illness (8 unipolar, mean age \pm SD: 50 \pm 10 years; 10 bipolar, mean age \pm SD: 45 \pm 10 years) and 7 control subjects; the patients were diagnosed with the Schedule for Affective Disorders and Schizophrenia instrument, the Research Diagnostic Criteria and the 24-item Hamilton Rating Scale. Patients were hospitalized for at least 15 days before the study and did not receive any medication during this interval. Blood sampling at 15-minute intervals lasted 25 hours. Both unipolar and bipolar depressed patients had significantly higher 24-h mean cortisol levels than controls, while no significant difference in the 24-h mean ACTH level was

found between depressed patients and controls. In addition, the nadir of cortisol secretion occurred almost 3 hours earlier in patients with unipolar depression, regardless of age, compared to young control subjects.³⁴

A more recent study including 15 severely depressed (mean \pm SD Hamilton Depression Scale score: 30.4 \pm 6.7) male inpatients (age 22-72 years) and 22 age-matched controls revealed significantly higher values of both mean 24-h cortisol and mean 24-h ACTH (24-h blood sampling with 30-minute intervals) in depressed patients than controls, independently of age. The frequency of cortisol and ACTH pulses during the evening were also higher in depressed subjects.³⁵ Increased cortisol levels have also been demonstrated in the urine and in the cerebrospinal fluid (CSF) of depressed men.³⁶

Sympatho-adrenal dysregulation is another common finding in depressed subjects, as evidenced by increased catecholamine turnover and increased catecholamine urinary excretion in severe depression.^{37,38}

The coexisting dysregulation of HPA and sympatho-adrenal axes in depression may result from a defect at or above the level of the hypothalamus, leading to hypersecretion of corticotropin-releasing hormone (CRH). Interestingly enough, ACTH response to exogenous ovine CRH is attenuated in depression, suggesting that the pituitary corticotroph cell is restrained by the negative feedback of glucocorticoids.³³ Moreover, a statistically significant increase of CRH has been reported in the CSF of depressed patients.³⁹ The positive correlation between CSF levels of CRH and CSF levels of norepinephrine and catecholamine metabolites in depression support the idea of a common central activation of HPA and sympathoadrenal axis by CRH.⁴⁰

Osteoporosis is a well-known consequence of both endogenous and exogenous glucocorticoid excess and hypercortisolism can be proposed as one of the mechanisms adversely affecting BMD in depressed patients. Bone loss occurs in 30 to 50% of patients under chronic treatment with corticosteroids and is more pronounced in trabecular than in cortical bone. Bone mass is only partially regained after remission of hypercortisolism, in a process that

can take many years.⁴¹

Gonadal axis

Low levels of sex hormones have been frequently observed in depressed patients. Moreover, plasma testosterone levels were negatively correlated with the severity of depression, after correction for age, in 15 male depressed patients.⁴² More recently, the association between endogenous sex hormone levels and depression has been evaluated in a large cross-sectional study on a cohort of community-dwelling older men. Participants included 856 men (age: 50-89 yrs) who, between 1984 and 1987, had attended a diabetes study clinic and who were not using testosterone therapy. Depression was assessed using 18 of the 21 items on the Beck Depression Inventory (BDI). Only 25 men in this cohort had clinical depression (BDI score equal to or higher than 13 and/or current use of antidepressant). The BDI score was significantly inversely associated with bioavailable testosterone and dihydrotestosterone, independently of age, weight change and physical activity, as demonstrated by linear regression and quartile analysis. Bioavailable testosterone levels were 17% lower in the 25 men with clinically diagnosed depression than levels in all other men. Neither total testosterone/dihydrotestosterone nor total or bioavailable estradiol was associated with depressed mood.⁴³ Another recent study reported significantly lower age-adjusted levels of daytime and nighttime testosterone and 24-hour mean testosterone in 15 male inpatients with moderate to severe major depression (diagnosed according to the DSM III-R criteria using a standardized interview) when compared to 22 healthy controls (age range: 22-85 years).⁴⁴

Hypogonadism is the best-characterized primary medical cause of osteoporosis in men. Cross-sectional studies demonstrated that bone mineral density is reduced in primary⁴⁵ and secondary hypogonadism.⁴⁶ Men treated with finasteride, which converts testosterone to dihydrotestosterone, do not have accelerated bone loss.⁴⁷

Somatomorphic axis

Altered stimulated and spontaneous growth hormone (GH) secretion has been reported in de-

pressed patients. A decreased nocturnal GH release and GH response to a combined releasing hormone test was found in 6 depressed men off medications compared to 6 age-matched healthy men.⁴⁸ In the same study, baseline GH levels (measured at 15-minute intervals over 26 hours) were lower in depressed patients compared to controls.

Another study comparing 11 medication-free patients (7 women and 4 men, mean age \pm SD: 53.2 \pm 11.6 years) diagnosed with primary endogenous depression (DSM-III and 21-item Hamilton scale) with 11 normal subjects matched for sex, age and body weight, found significantly reduced mean basal serum GH levels and attenuated net GH response to GH-releasing hormone (GHRH) in depressed patients compared to controls, and this reduction was independent of sex, age or body weight.⁴⁹ Analogous findings were reported in two other studies.^{50,51} It is not surprising that adult men with GH-deficiency often have reduced BMD.⁵²

Interleukin-6 (IL-6) and leptin

The first report of high plasma levels of IL-6 and its soluble receptor (sIL-6R) in depressed men was from a study comparing 77 major depressed subjects (36 men and 25 women, mean age \pm SD: 33.8 \pm 1.5 years; diagnosed with DSM-III-R and the 24-item Hamilton depression rating scale) with 38 healthy controls (21 men and 17 women, mean age \pm SD 36.6 \pm 1.3 years).⁵³ Analogous results were also reproduced by other groups.^{54,55}

More recently, lower nocturnal levels of leptin, a hormone secreted by the white adipose tissue, were reported in 62 depressed subjects (27 men, 35 women) compared to 64 controls (32 men, 32 women). The difference remained significant after adjustment for the covariates of BMI, age, medication and smoking.⁵⁶

Both IL-6 and leptin can influence bone metabolism. IL-6 and its receptor can modulate bone remodeling by regulating both osteoclast and osteoblast development and function.⁵⁷ Leptin has been proposed to inhibit bone formation through a hypothalamic relay.^{58,59}

PROPOSED ENDOCRINE MODEL OF BONE LOSS IN DEPRESSION

Prospective studies have associated depression and hip fractures.⁶⁰ In many cases, osteoporosis in men can be attributed to another disease;² however, in young adults, a major depressive episode was associated with lower BMD in men but not in women.⁶¹ Depression is involved in the pathogenesis of osteoporosis in a multifactorial and indirect fashion.⁶² We suggest that this mood disorder leads to hyperactivity of the HPA and sympatho-adrenal axes and suppression of the somatotrophic and gonadal axes, resulting in net bone loss (Figure 1).

The gender dimorphism in the epidemiology of both depression and osteoporosis is congruent with this hypothesis, with women patients showing a higher prevalence of both conditions than men. The fact that there are indications that the prevalence of osteoporosis in men may actually be higher than previously thought does not contradict this hypothesis, as there are ample indications that the prevalence of depression in men may also be higher than what has so far been considered.

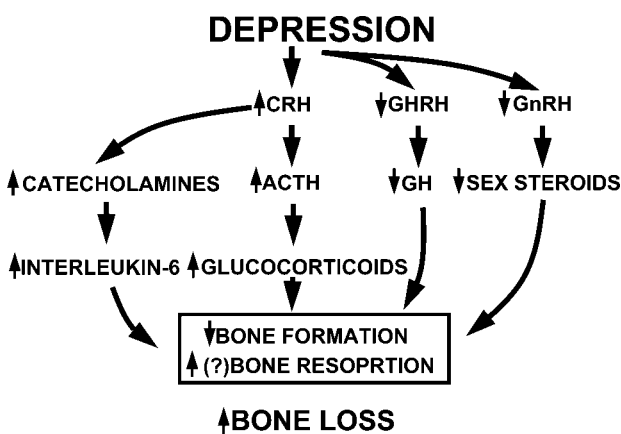


Figure 1. Depression leads to increased central CRH release, provoking higher ACTH and cortisol secretion, while lowered growth hormone (GHRH) and gonadotrophin-releasing (GnRH) hormone release from the hypothalamus suppress the secretion of GH and gonadal steroids, respectively. CRH also stimulates catecholamine release, inducing interleukin-6 production. The hyperactivity of hypothalamo-pituitary-adrenal and sympatho-adrenal axes, together with the suppression of somatotrophic and gonadal axes, result in primarily decreased bone formation, ultimately leading to net bone loss.

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