Osteoporosis and Depression: A Historical Perspective

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In the early 1980s, researchers studying osteoporosis noted that depression was one of the major negative consequences of bone loss and fractures. These researchers believed that osteoporosis and fractures occurred first, causing a reactive depression. Meanwhile, a similar but distinct psychiatry literature noted that osteoporosis or bone loss appeared to be an undesirable consequence of major depression. Here, depression was seen as the causal factor, and osteoporosis was the outcome. The psychiatric perspective is more biological, based on the presence of hypercorticoidism in depressed individuals. Those who believe that osteoporosis leads to depression point out that depression is a consequence of many chronic illnesses. Regardless of the correct causal order, the strong positive relationship between osteoporosis and depression merits further clinical and research attention in the future.

Introduction

Virtually all chronic medical illnesses have a negative impact on an individual's well-being and quality of life. Whether the primary physical outcome of the chronic illness is diminished function, unremitting pain, deformity, or comorbidity, devastating psychological and social outcomes proliferate as well [1]. Chronic diseases associated with later life may have several negative outcomes causing severe psychosocial anguish that may be expressed as depression [2]. Indeed, depression appears to be a reasonably predictable outcome for all chronic disease sufferers, regardless of patient age [3,4], social class [5], or race [6].

An association between depression and bone mineral density (BMD) is apparent despite the lack of prospective studies from which causal inferences may be drawn. In fact, little research has focused on the relationship between low BMD and depression. The research that has been done can be loosely divided into the psychosocial and biological paradigms. This article reviews the history of research on this potentially substantial relationship in hope of finding cumulative evidence to suggest a causal direction.

Osteoporosis

As defined by the 2004 Surgeon General's Report on Bone Health and Osteoporosis [7•], osteoporosis is a prevalent metabolic bone disease and results in bone fragility that ultimately leads to atraumatic bone fractures. Approximately 44 million Americans have this disease or are at high risk for it. Osteoporosis occurs most frequently in postmenopausal white and Asian women, but women of all races and older men can develop it as well. Factors that enhance an individual's risk of developing osteoporosis include older age, gender, family history, use of glucocorticoids (and other medication), lower body weight, and lifestyle factors such as smoking or drinking to excess [8]. The past several decades of pharmacologic research in the area of osteoporosis have resulted in the development of a number of drugs that improve bone density and reduce the likelihood of fractures. These drugs fall into two categories based on their mechanism of action: antiresorptive medications (alendronate, calcitonin, estrogen, ibandronate, raloxifene, and risedronate) and anabolic medication (teriparatide). Although some of these drugs are for prevention (estrogen) or treatment (calcitonin) only, the others (alendronate, ibandronate, raloxifene, and risedronate) are indicated for both uses. None of these drugs cure osteoporosis, and none can eliminate the potentially devastating consequences of the atraumatic fractures that seem inevitable with this disease.

In addition to the use of prescription medications, there are important nonpharmaceutical interventions to improve skeletal and overall health and to maximize quality of life for those who suffer from osteoporosis. Weight-bearing exercise and adequate daily intake of calcium and vitamin D are essential components of a successful management regimen [9]. With the ultimate goal of preventing fractures, people with fragile skeletons must also make lifestyle changes. Avoiding falls and

engaging in safe movement can reduce fracture risk substantially [10], as can compliance and persistence with prescribed medication [11].

Many women do not know that their bones have become fragile until they have their first atraumatic fracture; some are not aware even then. One fracture can be managed; two or more may lead to subsequent fractures and profound physical, economic, and psychosocial impact. This impact includes acute and chronic pain, height loss, substantial physical disability, and other factors commonly related to depression.

Depression

Depression is a relatively common but complicated psychiatric disorder, the etiology of which is multifactorial. Genetics, environment, and developmental issues all can contribute to this major public health problem [12]. The risk of depression is increasing rapidly in most developed countries, although there is no clear understanding of why this is true [13]. Many theories about the etiology of depression have been proposed, but none has been overwhelmingly supported. There is strong epidemiologic evidence, however, that women are at greater risk of developing depression than are men throughout the life course [14].

Osteoporosis and Depression: More than Coincidence?

Several decades have passed since the first studies of osteoporosis and of depression. We now have effective ways to measure BMD changes, to verify fractures, and to prevent and treat this bone disease, and new pharmacotherapeutic options have become available to manage the symptoms of depression. However, neither osteoporosis nor depression has a cure, and both diseases are more prevalent among women than among men. Two disparate research paths have approached the question of an association between these two chronic diseases. The first is based in the metabolic bone literature and has emerged from the perspective that depression is a response to osteoporosis. The second has emerged from the psychiatric literature and suggests a plausible theory that osteoporosis is the result of biologic changes caused by depression. Selected studies from these literatures are reviewed below.

Osteoporosis and depression: psychosocial perspectives

The presence of depression in patients with osteoporosis was first noted in the late 1980s in observational studies done in the context of osteoporosis education programs [15,16]. Each of these studies relied on convenience samples of older adult women with a physician diagnosis of osteoporosis who were participating in an educational intervention for their bone disease. In qualitative interviews, many of the respondents indicated that they felt *sad*, *dejected*, *downcast*, and *depressed*. When asked about the causes of these depressed feelings, many respondents indicated that the consequences of osteoporosis—chronic pain, deformity, inability to fill role expectations, and loss of control—resulted in more negative feelings. Although depression in these studies was defined as a global feeling of sadness, the fact that so many respondents with osteoporosis report feeling depressed indicates that the emotional consequences may come from the physical effects of osteoporosis.

Unfortunately, the data collected in these studies are not amenable to causal analyses because they are not longitudinal. It is clear, however, that the researchers hypothesized that subjects in this study developed osteoporosis, had fractures, and only then became depressed. That this hypothesized relationship cannot be tested is one major limitation of these studies. This assumption was consistent with early research in which the impact of other chronic diseases caused depression and anxiety for older adults.

Other experts also seemed to believe that osteoporosis was the cause and depression the response. In an editorial discussing ways to reduce the likelihood of hip fracture, Ford [17] reminds his readers (on page 269) that "One major complication of hip fracture that is all too often overlooked is depression." He also notes that better management of hip fracture, especially in the short term, might result in a reduction or elimination of depressive symptoms. Obviously, this editorial is not a presentation of empirical data, but the author nevertheless assumes that the hip fracture comes first, followed by depressive symptoms as a response to the osteoporosis and fracture.

During the 1990s, many reviews supported the idea that people with osteoporosis experienced fractures that led to chronic pain, deformity, functional limitation, and depression [18–21]. In early 2001, Robbins et al. [22] examined a random sample of 1566 Medicare enrollees who were participants in the longitudinal Cardiovascular Health Study. Total hip BMD was measured by dual energy x-ray absorptiometry (DXA); depression was measured using the 10-item Center for Epidemiologic Studies Depression Scale (CES-Dm) [23]. In uncontrolled analyses, depression was negatively related to total hip BMD for the whole cohort ($P < 0.001$), and among whites ($P < 0.01$) and African Americans ($P < 0.05$). After stratifying for race and gender, the negative relationship between total hip BMD and depression remained strong for white women ($P < 0.001$) but was not significant for other participants. Thus, studies continued to find a relationship between depression and bone loss in some populations but, from this perspective, did not disentangle the question of causation.

Depression and osteoporosis: psychiatric perspectives

As the psychosocial literature on bone loss and depression has emerged, a parallel literature has developed contemporaneously in the psychiatric arena. In the *American Journal*

of Psychiatry, Schweiger et al. [24] published an article entitled "Low lumbar bone mineral density in patients with major depression." This was one of the earliest studies on depression and bone loss. In it, the authors noted that both osteoporosis and depression are associated with hypercorticoidism. They expressed surprise that so little is known about BMD and major depression, especially given the high prevalence of both disorders in women. They compared bone density in 80 depressed inpatients aged 40 or older to that of 57 healthy adults with no history of major psychiatric disorders. Lumbar BMD was measured in both groups using CT. In a controlled analysis, the comparison group had significantly higher BMD than did the depressed subjects ($P < 0.001$). The authors concluded that they had identified depression as a new clinical risk factor for osteoporosis and that future research should include more heterogeneous samples.

This study did raise an interesting question. Are all patients with depression at risk of low bone density and osteoporosis, or does this risk apply only to those who take antidepressant medication? To test the impact of medication on psychiatric patients, Halbreich et al. [25] used dual-photon absorptiometry (DPA) to measure bone density in 68 physically healthy psychiatric inpatients (mean age, 39.4 years [SD, 11.8 years]; 33 female). The diagnoses for these patients were major depressive disorder ($n = 21$), schizophrenia ($n = 33$), schizoaffective disorder ($n = 7$), mania ($n = 2$), or adjustment disorder ($n = 5$). All patients were currently medicated with either antidepressants or neuroleptic agents; 10 were also treated with lithium. BMD was measured in the lumbar spine and the right femoral neck. Both men and women who had taken psychotropic drugs had significantly reduced BMD when compared with age- and sex-matched norms.

Another study on depression and BMD from the psychiatric perspective appeared in 1996 in the *New England Journal of Medicine*. Michelson et al. [26] enrolled 24 women with past or current depression and 24 matched controls without depression in their study. They then measured BMD in all the women at two sites in the spine, three in the hip, and at the radius, using DXA technology. The depressed women showed significantly lower bone density at all five hip and spine sites than the nondepressed women ($P \leq 0.02$). There was no significant difference in BMD at the radius ($P = 0.25$). Not only did these analyses highlight a significant relationship between BMD and depression; they also suggested that women with current or past depression might be at an increased lifetime risk for fractures because of the importance of their bone density losses.

Following the publication of this article, others continued to explore the depression-bone relationship from a psychiatric perspective. Coelho et al. [27] recruited a sample of 102 white, Portuguese women by random-digit dialing, excluding those who had received antidepressant medication. The women completed the Beck Depression Inventory and had BMD measurements in the lumbar spine and the femur, using DXA. The 48 women with osteoporosis (defined using the World Health Organization cutoff of a BMD equal to or less than –2.5 SD) reported having significantly more depressive symptoms than did the women with normal bone density (16 ± 9 vs 13 ± 10, $P = 0.045$). The overall prevalence of depression also was significantly higher among the osteoporotic women ($P = 0.024$).

Whooley et al. [28] examined data from a prospective, population-based cohort of 7414 white women at least 65 years of age. Spine and hip BMD were measured using DXA; depression was measured using the Geriatric Depression Scale. (Those whose scores were 6 or more were considered depressed.) The findings were somewhat unexpected, especially given the earlier literature: depressed women were significantly more likely to fall and to have a nonvertebral fracture ($P < 0.001$) than were nondepressed women, but there appeared to be no difference in BMD between the two groups ($P > 0.05$).

In an end-of-the-decade editorial, Dinan [29] reviewed the relationship between depression and its physical consequences and reiterated that the biological abnormality most frequently identified in the depression literature—hypercortisolism—has a profoundly negative impact on bone density. Citing the articles mentioned above by Schweiger et al. [24] and Michelson et al. [26], he concluded that it was time for health care professionals to recognize and try to prevent the physical consequences of depression and antidepressant medication, including the loss of bone density [29].

The Debate Continues

The 21st century has ushered in additional studies of the biologic links between depression and osteoporosis, with some added complexity and sophistication. Building on their earlier cross-sectional work [24], Schweiger et al. [30] measured follow-up BMD using quantitative CT on 18 depressed patients and 21 nondepressed patients who had participated in their earlier study [24]. In controlled analyses, the depressed patients sustained greater losses in BMD than did the nondepressed patients ($P < 0.01$). Surprisingly, the men showed greater bone loss than did the women in both the depressed and nondepressed groups. Despite the small sample size, this study made an important longitudinal contribution to the literature.

Investigators have begun to use bone markers to examine the relationship between bone remodeling and depression. In a cross-sectional study, Herrán et al. [31] compared 19 women experiencing a first depressive episode with 19 nondepressed women. Among the bone markers used were serum osteocalcin, type I collagen propeptide, bone-specific alkaline phosphatase, and parathyroid hormone (PTH). The results showed that serum osteocalcin, PTH, and C-terminal telopeptide (CTX) differed significantly between depressed and nondepressed

patients. It will be important to repeat this study with a larger, more heterogeneous sample and with subjects experiencing their second or later depressive episode.

In 2001, Cizza et al. [32] summarized the studies on depression and osteoporosis in an excellent review paper. They selected endpoints of BMD, falls, and fracture and found that the majority of studies showed a significant association between depression and osteoporosis (or bone density loss). Although most of the studies were cross-sectional, the study by Schweiger et al. [30] was longitudinal and the study by Whooley et al. [28] was a prospective cohort study over nearly 4 years. Of the seven studies reviewed, only two had results inconsistent with the finding of a positive association between depression and lower bone density. One of these was the study by Whooley et al. [28], who found significant increases in falls and fractures but no significant BMD differences between depressed and nondepressed women; this was quite different from the findings of others in the field. The second study was inconsistent because of the sampling decisions made by the investigators. Unlike the other studies, which focused on individuals with major depressive episodes, Reginster et al. [33] decided to look at women who were vulnerable to depression instead of those already diagnosed with full-blown depression. They evaluated 121 postmenopausal women who were being screened for osteoporosis at the University of Liège in Belgium. They used DXA to measure BMD of the spine and hip and the General Health Questionnaire (GHQ) to measure depressive vulnerability; there was no attempt to diagnose major depression in these women. In both uncontrolled and controlled analyses, no significant correlations between DXA score and GHQ score were found (all P values > 0.05). These findings suggest that the relationship between depression and bone loss occurs only in people with the disease, but the measure for depression is not an ideal one. Cizza et al. [32] ultimately recommended that patients with idiopathic bone loss should be screened for depression, just as depressed patients with a history of atraumatic fractures should be screened for osteoporosis.

Another study of BMD and depression was designed to evaluate the relationship between the two variables in a much younger group than is usually examined. Using data from the National Health and Nutrition Examination Survey III (NHANES III; N = 5171), Mussolino et al. [34] measured in young adults (aged 20 to 39 years) both BMD at the proximal femur (measured by DXA) and depression (measured using the Diagnostic Interview Schedule developed at the National Institute of Mental Health [35]). Data were collected between 1988 and 1994. These authors reported a unique finding: that a significant relationship existed between BMD and major depressive episode/dysthymia in young men (P = 0.02) but not in young women (P = 0.79). This gender difference was not seen in any of the earlier studies and may be influenced by the relative youth of this sample. The authors point out the importance of validating this unusual finding with a larger sample.

Mussolino himself [36] was interested in osteoporotic fractures in adults of all ages as serious threats to the public health and wondered whether the NHANES I data could provide insight into the relationship between hip fractures and depression. This cohort was a nationally representative US sample (N = 6195, aged 25 to 74 at baseline, which occurred from 1971 to 1975). They were followed for a maximum of 22 years. Hospital records and death certificates identified 122 cases of hip fractures. In an unadjusted model, depression was a significant predictor of hip fracture (HR = 1.90; 95% CI, 1.13–3.21; P = 0.016). When the model was adjusted for known risk factors for hip fracture, there was still a strong trend for depression as a predictor for hip fracture (HR = 1.70; 95% CI, 0.99–2.91; P = 0.055). These findings provide evidence of a prospective relationship between depression and hip fracture. Continuing studies along this line may help illuminate the biologic pathways by which depression has an impact on bone density.

Most of the studies reviewed here have been done in the United States. However, two non-US studies have examined the relationship between major depression and BMD, nonvertebral fractures, or both. Wong et al. [37•] reported findings from Mr. Os (Hong Kong), the first large cohort study of osteoporosis in Asian men. The sample included 1999 Chinese men, of whom 169 were depressed (score on the Geriatric Depression Scale ≥ 8). Mean age, weight, and BMD of the lumbar spine and the whole body (measured with DXA) did not differ significantly between the depressed and control men. These groups did differ significantly on total hip BMD (P < 0.01), daily calcium intake (P < 0.05), and score on the Physical Activity Score for the Elderly (PASE) scale (P < 0.05). This was the first study to show a significant association between BMD and depression in community-dwelling Asian men. Total hip BMD in the depressed subjects was 2.1% lower than in nondepressed subjects (95% CI, 0.13 to –4.1). The cross-sectional nature of this study and the fact that the subjects had no prospective depression or BMD data precludes any causal inference, but the findings in this non-US sample add strength to the assertion that depression is associated with BMD.

Finally, the Tromsø study, done in Norway, begins to address the lack of prospective cohort data for the examination of the relationship between depression and osteoporosis in both women and men [38]. A subsample of 4690 Tromsø residents were eligible for this study. Distal forearm BMD was measured in all participants using single x-ray absorptiometry (SXA). Each participant's nonvertebral fracture history was obtained from hospital radiographic archives. Depression was measured with a single item (Have you felt unhappy and depressed during the past couple of weeks?), for which there were four categorical responses ranging from "almost never" to "nearly all the time." Participants who answered with

the two highest categories were considered depressed for these analyses. This question was asked on three occasions and analyzed as cumulative exposure to feelings of depression. Women who reported being depressed at two time points had an adjusted odds ratio of 2.5 (95% CI, 1.3–4.9) for sustaining a nonvertebral fracture and of 3.1 (95% CI, 1.3–7.2) for sustaining an osteoporotic fracture, compared with women who reported never feeling depressed. Odds ratios for male subjects were not significant for either category of fracture. Although the risk of nonvertebral fracture was increased in this sample, no significant relationship between BMD and depression was evident in either women or men.

Of course, there are some obvious limitations to this particular study. Measurement of hip or spine BMD with DXA would have been preferable to measurement with SXA. The single-item measure of depression severely limited the type of depressed subjects who were identified. Replication with more valid measures is essential to better understand the relationships identified in this study.

Conclusions

Despite the work of investigators interested in depression, osteoporosis, or both, the literature on the relationship between these variables is limited; nevertheless, the findings in this area are fascinating. There is substantial empirical support for the idea that osteoporosis and fractures cause depression. There is also evidence that depressed people (especially those taking antidepressant medication) are at increased risk of osteoporotic fractures. The few longitudinal or prospective studies reported here provide additional support for this relationship.

One significant question remains: Which of these chronic diseases "causes" the other? Because of the need to gather prospective data over long periods to examine the causal relationship, it is unlikely that we will soon have the answer to this question. But it is clear that clinicians who provide osteoporosis care and management should recognize the importance of checking for depression in their patients, and those who treat major depression should be alert to any evidence of fractures, bone loss, or osteoporosis. Only then can the medical community begin to reduce the incidence of these comorbid conditions and improve the life quality of patients.

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