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REVIEW

Depression and osteoporosis: epidemiology and potential mediating pathways

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Abstract
Introduction There have been numerous studies examining the association between depression and bone mineral density (BMD), but the underlying nature of this relationship remains unclear. Independent of this association, there is a growing body of evidence that depression impacts the risk for fracture in older adults. This article reviews the current epidemiological evidence regarding comorbidity of depression, low bone mineral density, and fracture.
Methods A review of the literature on depression, depressive symptoms, low BMD, osteoporosis, and fracture using electronic databases.
Results We reviewed 20 studies of the association between depression and BMD and five reports of the relationship between depression and fractures. Potential mediating mechanisms (both physiological and behavioral) are discussed, as well as potential confounding influences (e.g., medication use).
Conclusions Most studies support the finding that depression is associated with increased risk for both low BMD and fractures, but variation in study design, sample composition, and exposure measurement make comparisons across studies difficult. Researchers should be aware of potential confounders, such as medication use, that may influence results. Future research should focus on identifying mediating pathways and targets for intervention in the relationships between depression, low BMD, and fracture.

Keywords Antidepressants · Behavior · BMD · Depression · Fracture · Physiology

This article reviews evidence regarding comorbidity of depression, low bone mineral density, and fracture, and potential mediating and confounding influences. Most studies report that depression is associated with an increased risk of osteoporosis and fractures. Potential mediating pathways include physiological and behavioral changes, comorbid medical conditions and medication use.

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Introduction

Osteoporosis was first recognized as a disorder of bone metabolism in a 1947 paper by Albright [1]. Since that initial publication, much has been learned about the physiology of bone turnover and how those mechanisms interact with other systems of the body. Numerous studies have demonstrated an association between antidepressant medication use and osteoporotic fracture [2], and it has been suggested that depression may be an unrecognized risk factor for osteoporosis [3]. This article reviews the current evidence regarding comorbidity of depression, low bone mineral density, and fracture, and discusses the unresolved issues regarding these associations, including potential mediating pathways and the potential confounding influence of medications.

Depression, depressive symptoms, and osteoporosis

Major depressive disorder (MDD) is one of the most prevalent psychiatric conditions, affecting approximately 16% of the U.S. adult population [4]. MDD is characterized by feelings of dysphoria and/or anhedonia accompanied by somatic (e.g., appetite or sleep disturbances) and cognitive (e.g., trouble concentrating) symptoms. MDD and depressive symptoms commonly co-occur with physical ailments [5]. Schweiger and colleagues published the first study examining the relationship between depression and bone mineral density (BMD) in 1994. They measured BMD by single-energy quantitative computerized tomography (SE-QCT) in 70 depressed outpatients (53 women) and 88 controls (58 women). They found that the depressed group had BMD values, on average, 15% lower than the control group, after adjusting for age [6]. The majority of analyses have replicated the original 1994 finding of Schweiger et al. lower BMD among persons with depression or depressive symptoms relative to comparison groups [7–18]. However, seven studies have not found a statistically significant association between depression or depressive symptoms and lower BMD [19–25]. These studies are discussed below under their respective study designs.

Cross-sectional studies

Seven studies have reported on the cross-sectional relationship between depression or depressive symptoms and BMD. As illustrated by Table 1, these studies have varied widely in both the selection of participants and measurement of depression. Three of these analyses have included only women [7, 9, 22] and two included only men [15, 23]. Six have used population or community-based samples [7, 9, 12, 15, 18, 23]. With the exception of Mussolino et al. (1999), these cross-sectional studies have used non-diagnostic symptom scales to assess depression status, which are less sensitive than diagnostic measures and presumably included persons only temporarily distressed in the "exposed" group. The confounding influences controlled for (either by statistical adjustment or matching) varied greatly, with few studies controlling for the effects of known confounding influences, such as comorbid medical conditions or medications that affect bone strength. Given the varied methods of measuring exposure, selecting study populations, and controlling for confounding variables, it is not surprising that results have been inconsistent. The majority of cross-sectional studies have found that depressive symptomatology was associated with lower BMD [7, 9, 12, 15, 18]. For example, using the third National Health and Nutrition Examination Survey (NHANES III), a nationally representative sample of U.S. adults, Mussolino et al. (2004) found that MDD (as measured by the Diagnostic Interview Schedule (DIS)) was associated with lower BMD, but this association was only statistically significant among men [18]. Two cross-sectional analyses did not find a statistically significant association between depressive symptomology and BMD [22, 23]; however, both studies had notable limitations. For example, the cross-sectional analysis of Whooley et al. (2004) was limited to 16 cases of elevated depressive symptoms and thus had limited power to detect a statistically significant effect [23]. In a cross-sectional analysis, Sogaard et al. (2005) reported no association between depressive symptoms (as measured by the CONOR Mental Health Index) and BMD, although the authors did not report the data for this analysis, and thus it is not described in the table. As shown by Table 1, the remaining five cross-sectional analyses reported an inverse association between elevated depressive symptomatology and lower BMD.

Case-control studies

Since the initial case-control study of depression and BMD reported by Schweiger and colleagues in 1994, nine additional case-control studies of this association have been published (Table 2). As with the cross-sectional reports, the selection of participants, exposure measurement, and consideration of potential confounders varied greatly. All but one [11] of the case-control studies relied on clinic populations to enroll participants. The use of clinic populations, risks the internal validity of study findings via selection bias, which could lead to false positive findings [26]. Assessment of depression varied across the studies and included depressive symptom scales (e.g., Centers for Epidemiologic Studies Depression Scale (CESD) or Geriatric Depression Scale (GDS)), structured diagnostic interviews (e.g., Diagnostic Interview Schedule (DIS) or Structured Clinical Assessment for Neuropsychiatry (SCAN)), and psychiatric diagnoses. Few studies accounted for the effects of medications known to influence bone strength (i.e., use of thiazide diuretics or hormone replacement therapy). As with the cross-sectional reports, results were inconsistent across these case-control analyses. Three of the ten case-control studies reported no association between depression or depressive symptoms and BMD [20, 21, 25]. Each of these studies had important limitations that should be taken into account when evaluating the evidence for this relationship. The case-control study by Amsterdam and Hooper (1995) had limited power to detect an effect given the small sample size (N=11) [20]. Similarly, the studies by Kavuncu et al. (2002) and Yazici et al. (2005) were limited to young pre-menopausal women (mean age of depressed group: 35.4 years and 44.8 years, respectively). Many of these women had not yet passed through the peak developmental period of risk for depression (age 30–

Table 1 Cross-sectional studies of depression or depressive symptoms and bone mineral density

First author	Year	Location	Sample size	Source of participants[a]	Measure of exposure[b]	Duration of exposure	Measure of BMD[c]	Matching and/or statistical adjustment	Main findings
Coelho [7]	1999	Portugal	102	Community sample (only women), age: 40–80 yrs	BDI HSCL-90	Current	Lumbar spine & femur DEXA	Adjusted for age and BMI	BMD≤−2.5 SD below reference mean (osteoporosis) assoc w/ higher DepSx
Reginster [22]	1999	Belgium	121	Outpatient clinic (only women), age: 48–77 yrs	GHQ	Current	Spine, total hip & femoral neck DEXA	Adjusted for age, menopause, weight, height, estrogen use	No assoc btw DepSx & BMD
Robbins [12]	2001	USA	1,566	Population-based Medicare enrollees, age: 65–100 yrs	CESD-10	Current	Total hip DEXA	Stratified by race and sex. Adjusted for age, BMI, kilocalories expended, estrogen use, smoking, alcohol intake	DepSx assoc w/ lower BMD overall DepSx assoc w/ lower BMD only among Caucasian women in stratified analyses
Mussolino [18]	2004	USA	5,171	Population-based, age: 30–39 yrs	DIS	Lifetime	Total proximal femur DEXA	Statified by sex. Adjusted for age, race, weight, height, food energy, calcium intake, protein intake, alcohol intake, smoking, physical activity, chronic conditions, weight change	*Men*: Major depressive episode assoc w/ lower BMD *Women*: No assoc btwn major depressive episode & BMD
Whooley [23]	2004	USA	515	Population-based (only men), age: 50+yrs	GDS	Current	Lumbar spine & total hip DEXA	Adjusted for age, weight change, physical activity, smoking, caffeine intake, calcium use, steroid, diuretic, & benzodiazepine use, perceived health, BMI, chair stand activity	No assoc btwn DepSx & baseline BMD
Wong [15]	2005	Hong Kong	2,000	Population based (only men), age: 65–92 yrs	GDS	Current	Lumbar spine, total hip & total body DEXA	Adjusted for age, weight, calcium intake, physical activity, antipressant use, smoking status, comorbid COPD and CVD	DepSx assoc w/ lower total hip BMD DepSx assoc w/ increased risk of T-score≤-1
Jacka [9]	2005	Australia	78	Community sample (only women), age: 45–60 yrs	Self-report DSM-based questionaire	≤ 1 year	Lumbar spine & total hip	Adjusted for age, weight, estrogen use	DepSx assoc w/ lower BMD

[a] Unless otherwise stated, studies include both men and women. Mean age of study participants is given if age range was unavailable.
[b] *Diagnostic measures of depression (MDD or MDE)*: *DIS* diagnostic interview schedule. *Non-diagnostic measures of depressive symptoms (DepSx)*: *BDI* Beck depression inventory, *HSCL-90* Hopkins symptom checklist-90, *GHQ* general health questionnaire, *CESD-10* centers for epidemiologic studies depression scale-10 item. *GDS* geriatric depression scale. Self-report DSM based questionnaire.
[c] *DEXA* dual-energy x-ray absorptiometry

Table 2 Case-control studies of depression or depressive symptoms and bone mineral density

First Author	Year	Location	Sample size	Source of participants[a]	Measure of exposure[b]	Duration of exposure	Measure of BMD[c]	Matching and/or statistical adjustment	Main findings
Schweiger [6]	1994	Germany	137	Inpatient clinic, community controls, age: 40–95 yrs	MDC	Current	Lumbar spine SE-QCT	Adjusted for age	MDD assoc w/ lower BMD compared to controls
Halbreich [8]	1995	USA	68	Inpatient clinic, age: 20–66 yrs	Psych Dx	Current	Lumbar spine & femoral neck DPA	Matched on age and sex	Psych Dx[d] assoc w/ lower BMD compared to age and sex-matched normative BMD data
Michelson [11]	1996	USA	48	Community volunteers (only women), mean age: 41 yrs	SCID	Past or current	Lumbar spine, hip & radius DEXA	Matched on 5-year age strata, BMI, menopausal status, race	MDD assoc w/ lower BMD compared to controls
Amsterdam [20]	1998	USA	11	Outpatient clinic, community controls, age: 27–53 yrs	Psych Dx	<1 yr to 25 yrs	Lumbar spine DEXA	None	No assoc btwn MDD & BMD
Vrkljan [14]	2001	Croatia	48	Inpatient clinic, community controls, age: 29–45 yrs	Psych Dx	Current	Unknown	None	Duration of depression therapy assoc w/ lower BMD
Kavuncu [21]	2002	Turkey	84	Inpatient clinic, community controls (only women), mean age: 36 yrs	Psych Dx HDRS	Current	Lumbar spine & hip DEXA	Matched on age and BMI	No assoc btwn MDD & BMD No assoc btwn DepSx severity & BMD
Yazici [16]	2003	Turkey	40	Outpatient clinic, community controls only women), mean age: 31 yrs	SCAN	Current	Lumbar spine & hip DEXA	Matched on age, BMI, calcium intake, physical activity, social class	MDD assoc w/ lower BMD
Yazici[25]	2005	Turkey	65	Outpatient clinic, community controls (only women), mean age: 45 yrs	Psych Dx HDRS	Current	Lumbar spine & femoral neck DEXA	Matched on age, BMI, age of menarche, number of pregnancies	No assoc btwn MDD & BMD
Kahl [10]	2005	Germany	58	Borderline PD[d] clinic, community controls (only women), mean age: 27 yrs	SCID	Current and Lifetime	Lumbar spine, femur & forearm DEXA	Matched on age and sex	MDD+borderline PD[d] assoc w/ lower BMD vs. borderline PD alone MDD + borderline PD assoc w/ lower BMD vs. neither
Altindag [17]	2007	Turkey	77	Outpatient clinic, community controls (only women), age: 26–56 yrs	Psych Dx HDRS	Current ≥ 3 months	Lumbar spine & femoral neck DEXA	Matched on age, BMI, age of menarche and parity	MDD assoc w/ lower BMD

[a] Unless otherwise stated, studies include both men and women. Mean age of study participants is given if age range was unavailable

[b] Diagnostic measures of depression (MDD or MDE): *MDC* Munich diagnostic checklist, *Psych Dx* psychiatrist diagnosis of major depressive disorder or major depressive episode. *SCID* structured clinical interview for DSM. *SCAN* structured clinical assessment for neuropsychiatry. *Non-diagnostic measures of depressive symptoms (DepSx): HDRS* Hamilton depression rating scale.

[c] *SE-QCT* Single-energy quantitative computerized tomography, *DPA* dual-photon absorptiometry, *DEXA* dual energy x-ray absorptiometry

[d] Psych Dx includes major depressive disorder, schizophrenia, schizoaffective disorder, mania or adjustment disorder

45) [27], and thus the cases of depression in these reports may not have been representative of the depression in the general population. It may be that depression affects BMD by accelerating post-menopausal bone loss in women, a hypothesis that neither of these studies could examine. However, Kavuncu et al. (2002) did find evidence of increased bone turnover, indicated by an elevated urinary deoxypyridinolie-to-creatine ratio, among the depressed group compared to controls [21]. The remaining seven case-control studies reported statistically significant inverse associations between depression and bone mineral density [6, 8, 10, 11, 14, 16, 17]. For example, Michelson et al. (1996) found that BMD as measured by DEXA was 13.6% lower at the femoral neck in women with a history of MDD compared to controls [11]. This study also found that depressed women had higher urinary cortisol levels than controls, a finding that supports the hypothesis that physiologic changes associated with depression, like hypercortisolism, mediate the relationship between depression and low BMD (discussed below).

Longitudinal studies

Schweiger and colleagues followed-up the study sample from their 1994 publication and in 2000 published a prospective study of depression and BMD.(13)]. They found evidence of increased bone density loss among the depressed group of men and women relative to the controls after two years of follow-up. The remaining three prospective studies of depressive symptomology and BMD (Table 3) have failed to replicate the Schweiger et al. (2000) finding [19, 23, 24]. It is difficult to compare these reports given the varied study populations and measures of exposure. The 1999 study by Whooley and colleagues was limited to post-menopausal women [24]; Sogaard et al. (2005) included both men and women (pre-and post-menopausal) [19]; and Whooley et al. (2004) included only elderly men [23]. While these three studies have the methodological strength of being population-based rather than clinic samples, all used non-diagnostic measures of depression, and thus it is likely that there is substantial heterogeneity in the "exposed" group in each of these studies, which would tend to bias the analytic results towards the null [28]. For example, Whooley and colleagues in 1999 and 2004 (while both studies are prospective, they are different study populations and the latter is not a follow-up of the former) measured depressive symptoms using the Geriatric Depression Scale [23, 24]. Similarly, Sogaard et al. (2005) used a three-item measure of "long-term mental distress" to measure exposure [19]. Also of note, the prospective analysis of the Whooley (2004) study was limited to four cases of elevated depressive symptoms and therefore had limited power to detect a significant relationship. Interestingly, while these studies did not find an association between depression and BMD, two of the studies that also measured incidence of fracture found that depression was associated with increased risk of osteoporotic fracture (discussed below) [19, 24].

Depressive symptoms and fracture

Even if depression does not directly affect BMD, it may still be an important risk factor for the clinically significant outcome of low BMD-fractures. Hip fractures are associated with dramatically elevated mortality during the first year after the event [29], and there is evidence that this excess mortality persists for many years after the event [29]. There have been far fewer studies of depression and fractures compared with depression and BMD, and the vast majority have been longitudinal. Because of the likely bi-directional nature of the relationship between osteoporotic fractures and depression, longitudinal studies provide a more transparent characterization this association than do retrospective (cross-sectional or case-control study) designs (Table 4). One retrospective study [30], and all but one of the five prospective studies[31] found significant positive associations between depression or depressive symptoms and risk of fractures [19, 24, 30, 32, 33]. The longitudinal study that did not find an association between depression and fractures nonetheless found an association between urinary cortisol and fracture; as discussed below, hypercortisolism is a well-documented physiologic correlate of depression [34].

The likelihood of fracture is determined by three factors: bone mineral density, the force of the fall, and the angle of impact [35]. It is controversial as to which of these factors mediates the relationship between depression and fractures, but as discussed above there is evidence that depression affects BMD and two studies have found increased risk of falling associated with depression [24, 36]. Thus it is likely that depression impacts the risk of fracture through multiple pathways.

Potential mediators

There are numerous mediating processes that may contribute to the relationship between depression and bone mineral density (Fig. 1). Two prominent ways in which depression is hypothesized to directly affect BMD and fracture risk are physiologic changes (e.g., alterations in the hypothalamic-pituitary-adrenal (HPA) axis) and the adoption of poor health behaviors (e.g., smoking and physical inactivity). It is also hypothesized that depression itself is not causally related to bone strength or fracture risk but is associated

Table 3 Comparative longitudinal studies of depression or depressive symptoms and bone mineral density

First Author	Year	Location	Sample size	Follow-up duration	Source of participants[a]	Measure of exposure[b]	Measure of BMD[c]	Matching and/or adjustment	Main findings
Whooley [24]	1999	USA	7,414	3.7 years	Population-based (only women), age: 65+yrs	GDS	Lumbar spine & hip DEXA	Adjusted for age, marital status, education, arthritis, diabetes, weight change, physical activity, smoking, alcohol use, caffeine intake, calcium use, BMI, estrogen, steroid, diuretic, and benzodiazepine use, perceived health, quadricepts strength	No overall assoc btwn DepSx & BMDDepSx assoc w/ lower BMD among highest BMI tertile vs. lower tertiles
Schweiger [13]	2000	Germany	39	2 years	Inpatient clinic, community controls, age: 40–95 yrs	MDC	Lumbar spine SE-QCT	Adjusted for baseline BMD, age, sex	MDD assoc w/ increased BMD loss at followup
Whooley [23]	2004	USA	100	3.6 years	Population-based (only men), age: 50+yrs	GDS	Lumbar spine & hip DEXA	Adjusted for age, weight change, physical activity, smoking, caffeine intake, calcium use, steroid, diuretic & benzodiazepine use, perceived health, BMI, chair stand activity	No assoc btwn DepSx & mean percent change in BMD
Sogaard [19]	2005	Norway	4,690	15 years	Population-based, age: 25+yrs	MDQ	Distal & ultradistal radius SXA	Stratified by sex; adjusted for age, marital status, BMI, receiving disability benefits, physical activity, smoking, estrogen use	*Women*: No assoc btwn DepSx & BMD *Men*: No assoc btwn DepSx & BMD

[a] Unless otherwise stated, studies include both men and women. Mean age of study participants is given if age range was unavailable.
[b] *Diagnostic measures of depression (MDD or MDE)*: *MDC* Munich diagnostic checklist. *Non-diagnostic measures of depressive symptoms (DepSx)*: *GDS* geriatric depression scale, *MDQ* self-report mental distress questionnaire.
[c] *DEXA* dual-energy x-ray absorptiometry, *SE-QCT* single-energy quantitative computerized tomography, *SXA* single-energy x-ray absorptiometry.

Table 4 Comparative longitudinal studies of depression or depressive symptoms and fractures

First Author	Year	Location	Sample size	Follow-up duration	Source of participants[a]	Measure of exposure[b]	Type of fracture	Fracture assessment	Matching and/or statistical adjustment	Main findings
Greendale [31]	1999	USA	684	7 years	Population-based, age: 70–79 yrs	HSCL-90	Hip, arm, spine, wrist & non-specified	Self-report of physician diagnosis	Adjusted for age, race, sex, comorbid conditions, physical activity, chair stand activity, BMI, smoking, alcohol use	No assoc btwn DepSx & fracture risk. Higher urinary free cortisol assoc w/ increased fracture risk
Forsen [33]	1999	Norway	18,612	3 years	Population-based (only women), age: 50–101 yrs	MDI	Hip	Medical record registry	Adjusted for age, medications, BMI, smoking, physical activity, functional impairment	Top 10% of mental distress assoc w/ increased fracture risk vs. lowest 10%
Whooley [24]	1999	USA	7,414	3.7 years	Population-based (only women), age: 65+ yrs	GDS	Non-vertebral & vertebral	Self-report confirmed by medical record radiographic films	Adjusted for age, marital status, education, chair stand activity, history of fracture, Hx of falling, arthritis, diabetes, steroid and estrogen use, calcium use, cognitive function, hip BMD	DepSx assoc w/ increased fracture risk (both vertebral & non-vertebral)
Sogaard [19]	2005	Norway	12,270	7 years	Population-based, age: 25+yrs	MDQ	Non-vertebral, hip, pelvis, proximal humerus, forearm	Hospital x-ray register; pathology reports to determine mechanism of trauma	Stratified by sex and nerve medications (women only); adjusted for age, marital status, smoking, alcohol use	*Women*: DepSx & DepSx + nerve meds assoc w/ increased fracture risk. *Men*: No assoc btwn DepSx & fracture risk
Mussolino [32]	2005	USA	6,195	18.3 years	Population-based, age: 25–74 yrs	GWBS	Hip	Hospital records & death certificates	Adjusted for age, sex, race, BMI, smoking, alcohol use, physical activity	DepSx assoc w/ increased fracture risk

[a] Unless otherwise stated, studies include both men and women. Mean age of study participants is given if age range was unavailable.
[b] *Non-diagnostic measures of depressive symptoms (DepSx)*: *HSCL-90* Hopkins symptom checklist-90, *MDI* mental distress index, *GDS* geriatric depression scale, *MDQ* self-report mental distress questionnaire *GWBS* general well-being schedule.

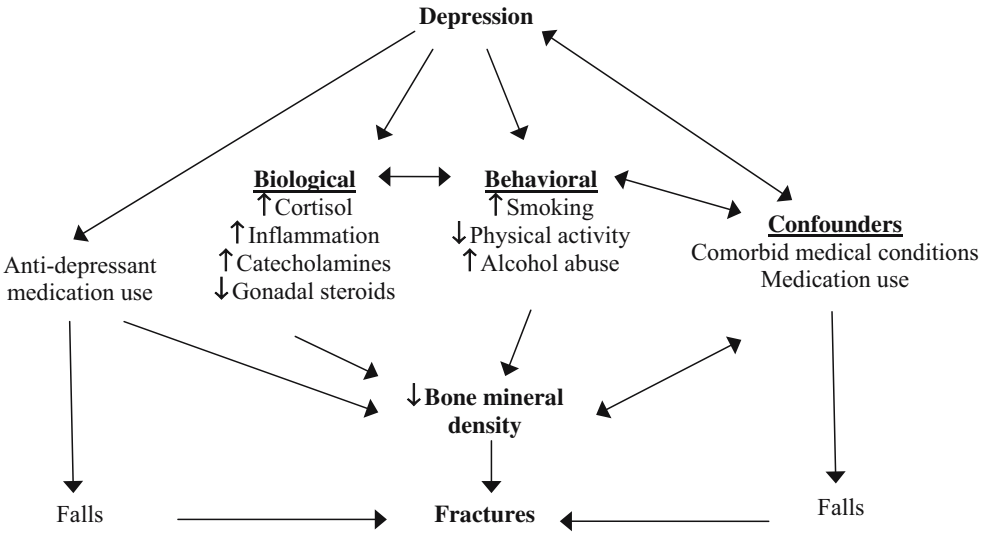

Fig. 1 Pathways linking depression, low bone mineral density, and fracture

with these conditions due to confounding influences of comorbid health conditions and use of medications that affect bone metabolism. As shown by the figure, these processes likely interact, and thus it is more appropriately characterized not as an absolutist question of whether a mediating path exists, but rather as a question of the *relative* importance of a given path at a particular point in development.

Physiology

There are three pathophysiologic pathways leading to low bone mineral density: (1) inadequate acquisition of bone mass early in life, (2) elevated resorption of bone mass later in life, and (3) inefficient bone formation during continuous bone remodeling [35, 37]. These pathways are interdependent and the relative importance of each mechanism changes over development and varies by sex.

Many neuroendocrine hormones affect bone formation and/or bone resorption. Elevated levels hormones that either increase osteoclast (bone resorption) activity (e.g., inflammatory cytokines interleukin-6 (IL-6), IL-1 and tumor necrosis factor-alpha (TNF-α), parathyroid hormone, and C-reactive protein (CRP)) or inhibit osteoblast (bone formation) activity (e.g., calcitonin, leptin and cortisol) are predicted to be associated with low BMD [38]. Levels of many of the hormones that influence bone metabolism are altered in depression. For example, hypercortisolism, a consequence of HPA axis activation, is a correlate of depression [34], and cortisol has potent effects on bone metabolism [39]. Levels of IL-6 [40] and other inflammatory markers, such as CRP [41], are elevated in depression, and elevated levels of these pro-inflammatory markers are associated with low BMD [41, 42]. Sympathetic nervous system (SNS) activity as measured by catecholamine synthesis and hormone levels (e.g., tyrosine hydroxylase, norepinephrine) [43, 44] is also elevated in depression, and levels of these hormones are associated with reduced BMD [38]. Hyperinsulinemia is also associated with depressed mood [45], and insulin is thought to preserve bone mass [46]. Depression is associated with decreased levels of gonadal hormones estrogen [47] and testosterone [48], which are key regulators of bone formation [49].

Depression stimulates the action of hormones that increase bone resorption (e.g., cortisol) as well as those that potentiate bone formation (e.g., insulin). However, there have been only three studies that have directly examined the effect of depression on markers of bone metabolism. Herran and colleagues (2000) compared markers of bone turnover between first-episode cases of MDD and controls and found that markers of bone turnover (e.g., osteocalcin, telopeptide, and cross-laps) were elevated in the cases versus the controls. They also found that hormones that affect osteoclast function (e.g., parathyroid hormone) and osteoblast function (e.g., cortisol) were altered in the cases compared to the controls [50]. Kahl et al. (2005) reported elevated levels of cross-laps, osteocalcin, cortisol, TNF-á and IL-6 among cases of comorbid MDD and borderline personality disorder compared to controls [10]. Finally, Altindag et al. (2007) found elevated levels of plasma cortisol and cross-laps and lower levels of osteocalcin among depressed outpatients relative to controls [17].

Behaviors

Depression is associated with many poor health behaviors that have physiologic consequences which affect BMD [51]. Depression is associated with smoking [52], which is associated with lower BMD by inhibiting estrogen activity and inhibiting calcium absorption by the intestines [53]. Depression is also associated with increased alcohol use [54], and chronic alcohol use is also associated with low BMD by inhibition of bone cell proliferation and function

[55, 56]. Depression is associated with fatigue and physical inactivity [57, 58], and physical activity is associated with increased BMD [36].

The association between depression and overall obesity as indicated by body mass index (BMI) is unclear and appears to be moderated by age, race and sex [59]. There is more consistent evidence regarding the positive association between depressive symptoms and abdominal or centralized obesity as measured by waist-hip-ratio [60, 61]. Body weight is positively associated with BMD [62] and is thought to preserve BMD by two mechanisms: first, synthesis of estrogen in adipose cells [63], which in turn promotes bone formation [35, 49], and second, through providing physical resistance to skeletal movement, which stimulates osteoblast activity [36]. The centralization of body weight is associated with alterations in markers of HPA axis and SNS dysregulation [64, 65]. Thus, while higher BMI may be protective of BMD loss with age, centralized obesity may be detrimental to bone mass because it is symptomatic of HPA hyperactivation, which inhibits bone formation and promotes bone resorption (discussed above).

Potential confounders

Comorbid medical conditions

Several medical conditions have been shown to affect risk of depression, bone mineral density, and fracture. Diabetes is associated with increased risk of depression [66], and diabetes (both type 1 and type 2) is associated with altered (both increased and decreased) BMD [67, 68]. Type 2 diabetes is more consistently associated with normal or increased BMD [69], whereas, type 1 diabetes is generally associated with decreased BMD [70]. Both types of diabetes are associated with increased risk of fractures [71, 72]. Other medical conditions associated with both depression and BMD include epilepsy [73], Crohn's disease [74], rheumatoid arthritis [75], and systemic lupus erythematosus [76]. Many of these associations are thought to be iatrogenic in nature due to the medications used to treat these conditions.

Medication use

Another potential confounder of the relation between depression and BMD is the use of medications that have the potential to affect either bone strength or risk of fracture. Several classes of medications are known to decrease bone mass: glucocorticoids (e.g., for treatment of autoimmune disorders) [75, 77], lithium [78], and anti-convulsants [79]. Other medications are known to increase bone mass: estrogen (e.g., postmenopausal hormone replacement therapy) [80], statins [81], and thiazide diuretics [81].

Bone mineral density and antidepressant medications

Seven studies that examined the relationship between depression and BMD controlled for the influence of antidepressant medication use, either by statistical adjustment or exclusion criteria (Tables 1, 2, 3). Both studies that used statistical modeling methods found that the association between depression and low BMD persisted after adjusting for antidepressant use [11, 15]. Three studies only included cases that had a history of antidepressant use [8, 11, 12], and all found that depression was associated with decreased BMD. Two studies only included cases that had never used antidepressant medications [7, 16], and both found that depression was associated with risk of osteoporosis. One study found an inverse association between years of unspecified depression therapy and BMD [14].

There have been few studies of the direct effects of antidepressant medications on bone turnover. Studies have found that phosphodiesterase inhibitors, which are approved as antidepressant treatments in the UK but not in the US, increase bone formation in animal models [82, 83]. Animal studies have also indicated that serotonin may influence bone mass, particularly during stages of bone growth [84, 85]. A recent study showed that daily injections of the selective serotonin reuptake inhibitor (SSRI) fluoxetine in mice increased bone formation relative to controls, but that this effect was not observed in estrogen-deficient animals [86]. However, these initial results have not been replicated [87]. These results suggest that the effect of antidepressants on bone metabolism may depend on developmental stage and sex steroids (e.g., menopausal status in humans).

Five studies have directly examined the relationship between antidepressants and BMD in humans, with the majority reporting that use of these medications is associated with BMD. An analysis of the NHANES III data by Kinjo and colleagues found no association between antidepressant use and BMD [79]. However, Cauley and colleagues found that current use of SSRIs, but not tricyclic antidepressants (TCAs), was associated with low lumbar and hip BMD [88]. This finding that the association between antidepressant use and BMD is restricted to the SSRI class of antidepressants has been supported by the findings of two recent studies by Diem et al. (2007) [89] and Hanley et al. (2007) [90]. Notably, the study by Diem and colleagues found that the association between SSRI use and BMD persisted even after adjustment for depressive symptoms as measured by the geriatric depression scale. Another recent study of SSRI use in a prospective population-based cohort found that daily SSRI use at baseline was associated with 4% lower total hip BMD at followup five years later [91].

While this latter study controlled for depressive symptoms (as measured by the Short Form-36) they did not have a diagnostic measure of depression [91]. In sum, none of the currently published studies of antidepressant use and BMD have adjusted for depression as measured by a diagnostic or clinical instrument, and subsequently it is unclear whether this association is an example of confounding by indication. In light of the apparent association between antidepressant use and fracture (discussed below), it remains unresolved as to whether antidepressant medications increase the risk of fracture by directly reducing BMD as opposed to simply impairing balance and concentration, thus increasing the likelihood of falls.

Fractures and antidepressant medications

Numerous studies have examined the association between antidepressant use (both SSRIs and TCAs) and fracture risk. The majority have found that use of these medications, regardless of class (i.e., SSRI, TCA) is associated with increased risk of fracture [2]. However, most of these studies did not control for depression or depressive symptoms, and thus these analyses beg the question of whether the association between antidepressant use and fractures is due to confounding by indication. Those studies that did adjust for depressive symptomology found that the association between antidepressants and fracture was attenuated when depression was included in the model [92]. Studies that have examined duration of antidepressant medication use have shown that current use of these medications is a stronger predictor of fractures than former use [93–95], which indicates that these medications may be a more important confounder regarding the risk of falling or fracture than any effect they may have on BMD, since antidepressants often take weeks to significantly alter cell metabolism [96].

Three prospective studies of depression and fracture (Table 4) have adjusted for use of sedative and/or antidepressant medications, and all found that depression is associated with increased risk of fracture after taking the effects of such medications into account [19, 24, 33]. Thus it is possible that studies examining the relationship between antidepressant medications and fracture may overestimate the risk associated with these agents if they fail to adjust for indexes of depression [33].

Conclusion

Low bone mineral density (BMD) is a common condition among older adults, and the prevalence of osteopenia and osteoporosis is expected to increase dramatically in the next 50 years as the population pyramid shifts toward old age. Low BMD is associated with pronounced increased risk for debilitating fractures, particularly of the hip, vertebrae and distal forearm. Many of the prominent risk factors for low BMD, such as sex, age, race/ethnicity, and body type, are unalterable. It is therefore crucial to identify modifiable risk factors in order to reduce the public health burden of osteoporosis and osteopenia and the fractures associated with them.

Major depressive disorder is a common psychiatric disorder that is treatable with pharmacological and/or cognitive-behavioral therapy. Depression has been shown to be associated with low BMD in several studies, but even if depression influences BMD, it is unclear whether those changes are *clinically* meaningful. Depression has also been associated with increased risk of fractures. It is possible that depression affects the risk of low BMD and associated fractures in multiple ways, through both physiologic and behavioral mechanisms, and it is crucial to account for potential confounding influences, including antidepressant medications, when examining this relationship. Future studies should focus on establishing the mediating pathways that connect depression to fracture risk, in hopes of identifying targets for intervention and prevention.

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