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Bone mineral density and bone metabolism in patients with major depressive disorder without somatic comorbidities

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ABSTRACT

Background: Major depressive disorder (MDD) has been linked with accelerated bone loss leading to the development of low bone mineral density (BMD). Several mechanisms have been discussed as causative factors, e.g. lifestyle, selective serotonin reuptake inhibitor (SSRI) intake, or the influence of proinflammatory cytokines.
Methods: In a cross-sectional study of in-patients with a current episode of MDD, without somatic comorbidities, we determined various parameters of bone metabolism, inflammatory parameters and parameters of depression. BMD was measured by dual x-ray absorptiometry.
Results: Of 50 patients, only one had low BMD in any of the measure sites. Body mass index (BMI) correlated positively with Z-scores. 83.3% of the examined patients had elevated osteoprotegerin (OPG) levels. SSRI intake did not have an effect on BMD. BMD in the femoral neck was significantly lower in smokers. We also found a positive correlation between the level of physical activity and osteocalcin levels.
Conclusions: In our sample, young to middle-aged, somatically healthy, and acutely depressed patients with a history of MDD showed no reduction of BMD. This could be due to compensatory mechanisms, as suggested by elevated OPG levels. Physical activity and high BMI could also have served as protective factors. Still, as patients with MDD often suffer from comorbidities or take medication with a negative effect on bone, this population should be appreciated as a high-risk group for the development of osteopenia and osteoporosis.

1. Introduction

Major depressive disorder (MDD) is a common psychiatric disorder with lifetime prevalence of up to 16.2% in the U.S. (Kessler et al., 2003). According to the WHO, it is also considered to be the leading global cause of years of life lived with a disability. Approximately half of the patients with depression have at least one comorbid psychiatric or somatic medical condition that worsens the prognosis and contributes to the high rate of morbidity and mortality (Moldin et al., 1993). Numerous studies have found MDD to be associated with accelerated bone loss leading to the development of low bone mineral density (BMD) or osteoporosis. These findings have also been acknowledged by a meta-analysis conducted by Yirmiya and Bab (2009). Several pathophysiological mechanisms have been discussed as causative factors of low BMD. Petronijević et al. (2008) found elevated markers of bone resorption in premenopausal depressive women with low BMD, pointing towards an overbalance in favor of bone resorption versus bone formation in patients with affective disorders. Decreased BMD also correlated with the duration of depression.

Studies investigating the effect of antidepressants, in particular selective serotonin reuptake inhibitors (SSRIs) on bone metabolism have yielded divergent results. SSRI use has been associated with low BMD (Cauley et al., 2005; Haney et al., 2007; Williams et al., 2008) and increased rates of bone loss (Diem et al., 2007). Others have failed to show this association, while still reporting reduced BMD in depressive patients (Michelson et al., 1996). There has also been some evidence that SSRI intake leads to an increased risk of fracture, although a meta-analysis by Wu et al. (2012) revealed that this risk stands independent of BMD and is perhaps related to an increased risk of falls. A recently published study by Aydin et al. (2011) even showed a beneficiary effect of the SSRI escitalopram, at least on

Abbreviations: MDD, major depressive disorder; BMD, bone mineral density; SSRI, selective serotonin reuptake inhibitor; BMI, body mass index; OPG, osteoprotegerin; IPAQ, International Physical Activity Questionnaire; CRP, C-reactive protein; IL-6, interleukin-6; RANKL, receptor activator of nuclear factor-κB ligand; MINI, Mini-International Neuropsychiatric Interview; IDS-C, Inventory of Depressive Symptoms; MADRS, Montgomery–Asberg Depression Rating Scale; HAMD, Hamilton Depression Scale; BDI, Beck Depression Inventory; DXA, dual x-ray absorptiometry; PTH, parathyroid hormone; 25OHD, 25-hydroxyvitamin D; OC, osteocalcin.

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bone formation in female patients, although BMD was not measured in this study and therefore could not be taken into consideration.

Interestingly, various increased anti-inflammatory and pro-inflammatory cytokines have been implicated to influence osteoclastic bone resorption (Ershler and Keller, 2000) resulting in a decreased BMD as well. Several studies have reported an increase in pro-inflammatory markers like C-reactive protein (CRP) and interleukin-6 (IL-6) in depressive disorders (Marques-Deak et al., 2005). Another interesting parameter in this context is osteoprotegerin (OPG), a soluble member of the tumor necrosis factor receptor superfamily. The OPG–RANKL–RANK axis has been shown to have pleiotropic effects on bone metabolism and the immune system. OPG has been associated with the prevention of bone loss (Trouvin and Goëb, 2010). It inhibits osteoclastogenesis by binding the receptor activator of nuclear factor-κB ligand (RANKL), acting as a decoy receptor to competitively inhibit RANKL interaction with its receptor RANK, therefore serving as bone-protective factor. IL-6 is known to elevate RANKL (and subsequently – as "counteraction" – elevate OPG levels) (Theoleyre et al., 2004).

Low vitamin D levels have also been found in depressive patients (Eskandari et al., 2007), which could contribute to BMD reduction. Other possible pathways leading to low BMD in depressive patients are excessive smoking (Kapoor and Jones, 2005), secondary alcohol consumption (Chakkalakal, 2005; Malik et al., 2009) and dietary deficiencies with low body mass index (BMI). In various studies, a low BMI has been shown to be a risk factor for osteoporosis and subsequent fractures (Ravn et al., 1999). A low BMI through reduced appetite and weight is common in MDD patients.

Physical activity also has a significant impact on bone. It can regulate bone maintenance and stimulate bone formation, including the accumulation of minerals (Borer, 2005). Low physical activity, often present in depressed patients (Camacho et al., 1991), has been discussed to be a risk factor for low BMD (Diem et al., 2012; Korpelainen et al., 2006). However, many of the studies in the field have not excluded somatic comorbidities, which can contribute to a disturbed bone metabolism and therefore lead to reduced BMD.

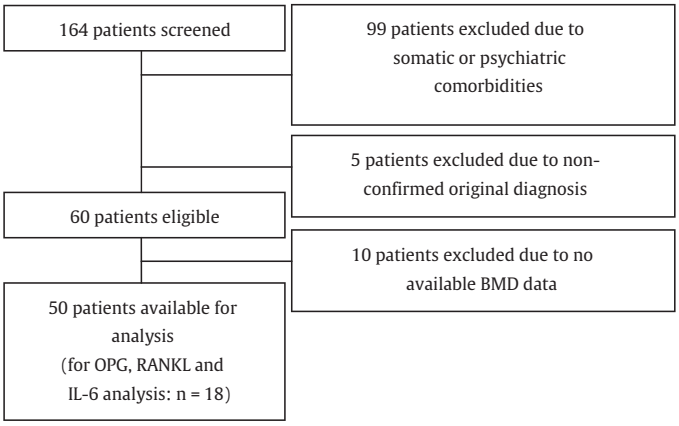
The following questions were investigated in this cross-sectional-study:

- Can we confirm earlier findings in depressed patients showing reduced BMD?
- If so, is this associated with an elevation of OPG-levels and IL-6-levels, respectively?
- Is BMD associated in any way with the severity of depression or the number of depressive episodes?
- Can any association with other inflammatory parameters be found?
- In addition to the points above, can we confirm the already established influence of medication (SSRI in history vs. no SSRI), physical exercise, or smoking on BMD in depressive patients?

2. Methods

As part of the "Early diagnosis, treatment and prevention of mood disorders targeting the activated inflammatory response system" (MOODINFLAME) study, a multicenter study focusing on inflammatory processes in affective disorders, we recruited in-patients with a current episode of major depression in the Department of Psychiatry of the University Hospital Innsbruck (flowchart see Table 1). The study was approved by the Ethics Committee of Innsbruck Medical University. Recruitment was conducted by trained psychiatrists. Patients with somatic comorbidities which could have influenced bone metabolism, as well as medication with a potential negative effect on bone, with the exception of antidepressants, were excluded from the study. Postmenopausal women were also excluded. Histories of psychiatric comorbidities such as anxiety disorders or substance abuse were also exclusion factors. Diagnosis of MDD was verified by the Mini-International Neuropsychiatric Interview (MINI). After a thorough study description, informed consent was obtained. A thorough investigation of depressive symptoms was performed by a trained psychiatrist using the Inventory of Depressive Symptoms (IDS-C), the Montgomery–Asberg Depression Rating Scale (MADRS) and the Hamilton Depression Scale (HAMD). The Beck Depression Inventory (BDI) was used by patients' self-rating. Furthermore, we evaluated the duration of illness by self-report, the patients' medical records, as well as their history of somatic diseases. Information to determine the amount of physical activity prior to inpatient treatment was obtained by using the long version of the International Physical Activity Questionnaire (IPAQ). This self-report questionnaire has been validated to be useful to monitor levels of physical activity among 18 to 65-year-old adults in various settings.

Table 1
Flowchart of the screening process.



In the same week as the consent process and the interview were undertaken, we determined BMD by dual x-ray absorptiometry (DXA) with a QDR*4500-Hologic densitometer in the lumbar spine (L1–L4) and the proximal right femur (femoral neck, total hip). BMD of individual patients was compared to a normative curve (obtained using data of a reference population included in the Hologic densitometer) and computed as Z-score (standardized difference from the mean) to enable comparisons of values across age and sex. A Z-score of −2.0 or lower is defined as "below the expected range for age" (The International Society for Clinical Densitometry — ISCD: 2007 official positions). Precision data from the densitometer are obtained via daily quality control by medical–technical personnel, highlighted through a so-called correlation variable (CV) with a value of approximately 0.4 (referring to variability of 0.4% or lower between two separate measurements).

Also in the same week of the interview, patients had blood drawn in the morning for the analysis of liver function tests, calcium, phosphate, parathyroid hormone (PTH), 25-hydroxyvitamin D (25OHD), osteocalcin (OC), serum CrossLaps, sex hormones (estradiol, testosterone) and prolactin. OPG, RANKL and IL-6 were also measured. Vitamin D insufficiency is defined as a 25OHD concentration from 50 to 74 nmol/l, whereas deficiency is defined as a 25OHD level less than 50 nmol/l (Holickm, 2009).

2.1. Statistical analysis

Patient characteristics are given as percentages, means, standard deviations and ranges. BMD of individual patients was compared with a normative curve and computed as a Z-score (difference from the mean, divided by the standard deviation) to enable comparisons