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

P. Malik a,⁎, R.W. Gasser d, R.C. Moncayo c, C. Kandler a, P. Koudouiovoh-Tripp b, J. Giesinger b, B. Sperner-Unterweger a

a Department of Biological Psychiatry, Medical University, Anichstrasse 35, 6020 Innsbruck, Austria. b Department of Internal Medicine, Medical University, Anichstrasse 35, 6020 Innsbruck, Austria. c Department of Nuclear Medicine, Medical University, Anichstrasse 35, 6020 Innsbruck, Austria. d Department of General Psychiatry, Medical University, Anichstrasse 35, 6020 Innsbruck, Austria.

⁎ Corresponding author at: Department of Biological Psychiatry, Medical University Innsbruck, Anichstrasse 35, 6020 Innsbruck, Austria. Tel.: +43 512 504 25267. E-mail address: Peter.Malik@med.ac.at (P. Malik).

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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.

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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
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 osteoelastic 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 (Trouw and Goeb, 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 (HAM-D). 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.

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 (Holickl, 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...
3. Results

164 patients were screened for participation in the study; 104 patients had to be excluded due to various somatic or psychiatric comorbidities. For 10 patients, data on BMI was not available due to drop-out, leaving 50 patients for analysis of BMI. Analysis of some laboratory parameters was also based on a smaller sample size as some patients dropped out after the assessment of BMI, but prior to blood collection. OPG, RANKL and IL-6 were determined in both groups with Cohen’s d = 0.81 (two-sided, alpha = 0.05, beta = 0.20).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Z-score</th>
<th>Statistics (comparison with Z = 0)</th>
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<td>L1–L4</td>
<td>0.09</td>
<td>0.25 1 0.50 49 0.620</td>
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<td>Femoral neck</td>
<td>0.01</td>
<td>0.92 0 0.11 49 0.915</td>
</tr>
<tr>
<td>Total hip</td>
<td>0.15</td>
<td>0.84 0 1.28 49 0.207</td>
</tr>
</tbody>
</table>

BMD: Bone mineral density.

4. Discussion

In the present study, we endeavored to confirm that patients with MDD suffer from reduced BMD, focusing on young and middle-aged patients. Furthermore, we tried to examine the influence of different mechanisms, both behavioral and on a cellular level, as well as the duration of depression, on BMI. As the patients were included as part of the MOODINFLAME study and therefore did not have any somatic comorbidities nor a history of medication which could influence bone metabolism, we suggest that our sample reflects a relatively unbiased view on younger patients with MDD without too many confounding factors having a negative impact on bone. Furthermore, our patient sample sufficiently covers a whole range of BMI values as well as different lengths of duration of depression.

In contrast to many studies in the field, we did not find a significant reduction in BMI in patients with MDD. Recent, three meta-analyses (Cizza et al., 2010; Wu et al., 2012; Yirmiya and Bab, 2009) concluded that depression should be considered to be an important risk factor for osteoporosis. Still, existing data concerning this issue is by no means consistent. Several studies have already failed to show diminished BMD in depressive patients (Amsterdam and Hooper, 1998; Kavuncu et al., 2002; Reginste et al., 1999; Seggaard et al., 2005; Whooley et al., 1999; Whooley et al., 2004; Yazici et al., 2005), which is even more understandable when looking at the heterogeneity of the examined patients in these reports. In a number of those studies, power limitations may restrict the interpretation of some of the results. A few have used non-diagnostic symptom scales to assess depression status and may therefore have included patients without a correct diagnosis of MDD. Also, as shown in the meta-analysis by Yirmiya and Bab (2009), rating by a clinician, not self-rating, showed strong correlations between depression and reduced BMD. Still, the question remains why the patients in our sample show different results than one might expect. The lower patients’ age in our study than that in other studies in the field might play a role.

We also found a positive correlation between BMI and Z-scores in all regions, confirming earlier reports. Body weight, also reflected by BMI, has been reported to be positively associated with BMD (Dargent-Molina et al., 2000). This may be due to two mechanisms: firstly, promotion of bone formation through pronounced synthesis of estrogen in adipose cells and secondly stimulation of osteoblast activity through load exercise. As only one of the included patients had a low BMI, and 36.1% of patients had a higher than normal BMI, this could have served as a protective factor and thus explain the mostly normal BMD.

Bone formation and resorption, determined by OC and CrossLaps, were outside the normal range only in a small number of patients, indicating a relatively stable bone metabolism in our sample. In a recent report by Aydin et al. (2011), OC levels increased and CrossLaps levels decreased after a three-month antidepressant therapy. None of our patients had a history of less than two months of antidepressant treatment. Table 3 shows that the scales we used, was high, with e.g. a mean score in MADRS of 27.5. Correlations of BMD with BMI, parameters of depression, physical activity, and selected laboratory parameters are shown in Table 4. Low levels of 25-OH-vitamin D3 could be found in 74.5% of the patients. Elevated activity, and selected laboratory parameters are shown in Table 3.

Table 2

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BMD: Bone mineral density.
therapy prior to our examination, but we still could not observe the effects shown in their study.

SSRI use has been associated with reduced BMD in both males and females (Tsapakis et al., 2012). This may be linked to direct and indirect serotonin (5-HT) effects on bone cells, e.g. through decreased osteoblast proliferation through gut-derived 5-HT (Yadav et al., 2008). It appears that the negative skeletal effects of peripheral SSRI-induced increase in 5-HT outweigh the skeletal benefits resulting from the enhanced central 5-HT antidepressant and antisym pathetic activity. A meta-analysis by Wu et al. (2012) examining thirteen studies in the field, showed an increased risk of fracture related to SSRI therapy. In our study, no differences in BMD between patients with and without a history of SSRI intake could be found, although admittedly the case number of the latter group was quite small. Nevertheless, this corroborates a study by Kinjo et al. (2005), who could also not find any significant association between SSRI use and BMD levels in the femur, again pointing to a negative influence of tobacco on BMD which has already been described in various studies (Hopper and Seeman, 1994).

Physical inactivity has been described to be common in depressive patients. Evidence to support an effect of physical inactivity on bone metabolism has been reported (Ho and Kung, 2005; Korpe lainen et al., 2006). Information on physical activity in studies focusing on depressive patients and BMD has been rare, with Petronijevi et al. (2008), which showed a correlation between duration of depression and reduced BMD in contrast to our findings. On the other hand, Schweiger et al. (1994) did not find a relationship between BMD and the number of depressive episodes as well. Patients with a history of smoking showed significantly decreased Z-scores in the femur, again pointing to a negative influence of tobacco on BMD which has already been described in various studies (Hopper and Seeman, 1994). Physical inactivity has been described to be common in depressive patients. Evidence to support an effect of physical inactivity on bone metabolism has been reported (Ho and Kung, 2005; Korpelainen et al., 2006). Information on physical activity in studies focusing on depressive patients and BMD has been rare, with Petronijevi et al. (2008) reporting correlations between reduced physical activity and markers of bone resorption, using the Quality of Life Questionnaire of the European Foundation for Osteoporosis. The IPAQ, a self-rating instrument that we used to evaluate the week prior to our examination, serves as an ef ficient instrument when trying to quantify the level of exercise. As the patients in our study were acutely depressed studies in the field, our patients had to be acutely depressed to be included into the study. A similar design was undertaken by Petronijević et al. (2008), which showed a correlation between duration of depression and reduced BMD in contrast to our findings. On the other hand, Schweiger et al. (1994) did not find a relationship between BMD and the number of depressive episodes as well. Patients with a history of smoking showed significantly decreased Z-scores in the femur, again pointing to a negative influence of tobacco on BMD which has already been described in various studies (Hopper and Seeman, 1994). Physical inactivity has been described to be common in depressive patients. Evidence to support an effect of physical inactivity on bone metabolism has been reported (Ho and Kung, 2005; Korpe lainen et al., 2006). Information on physical activity in studies focusing on depressive patients and BMD has been rare, with Petronijevi et al. (2008) reporting correlations between reduced physical activity and markers of bone resorption, using the Quality of Life Questionnaire of the European Foundation for Osteoporosis. The IPAQ, a self-rating instrument that we used to evaluate the week prior to our examination, serves as an efficient instrument when trying to quantify the level of exercise. As the patients in our study were acutely depressed

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Table 4

<table>
<thead>
<tr>
<th>Parameter (normal range)</th>
<th>Mean ± SD</th>
<th>Range</th>
<th>Median/IQR</th>
<th>Lowered</th>
<th>Normal</th>
<th>Elevated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone (m: 2.8–7; f: 0–0.4 μg/l)</td>
<td>1.34 ± 1.90</td>
<td>0.16–7.40</td>
<td>0.21/2.95</td>
<td>0</td>
<td>0</td>
<td>43</td>
</tr>
<tr>
<td>Osteocalcin (15–46 μg/l)</td>
<td>20.68 ± 6.29</td>
<td>9.20–37.10</td>
<td>20.48/6.8</td>
<td>3</td>
<td>6.7%</td>
<td>39</td>
</tr>
<tr>
<td>CrossLaps (30–440 ng/l)</td>
<td>246.7 ± 145.4</td>
<td>72.0–989.0</td>
<td>220.0/124.0</td>
<td>0</td>
<td>0</td>
<td>44</td>
</tr>
<tr>
<td>Prolactin (1.9–25 μg/l)</td>
<td>15.76 ± 23.66</td>
<td>2.70–149.00</td>
<td>8.6/7.20</td>
<td>0</td>
<td>0</td>
<td>39</td>
</tr>
<tr>
<td>CRP (0.86–2.84 mg/ml)</td>
<td>3.79 ± 0.82</td>
<td>2.50–5.40</td>
<td>3.80/3.10</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>RANKL (0–0.71 pmol/l)</td>
<td>0.13 ± 0.17</td>
<td>0.02–0.69</td>
<td>0.10/0.04</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IL-6 (0–15 ng/l)</td>
<td>2.09 ± 0.23</td>
<td>2.00–2.70</td>
<td>2.00/0.00</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CRI (0–0.7 mg/dl)</td>
<td>6.20 ± 0.18</td>
<td>0.04–0.72</td>
<td>0.14/0.22</td>
<td>0</td>
<td>0</td>
<td>47</td>
</tr>
<tr>
<td>PTH (15–65 ng/ml)</td>
<td>33.92 ± 14.94</td>
<td>14.00–92.80</td>
<td>32.00/19.10</td>
<td>1</td>
<td>2.1%</td>
<td>44</td>
</tr>
<tr>
<td>17-Beta estradiol (μg/l)</td>
<td>74.19 ± 101.76</td>
<td>12.00–516.00</td>
<td>41.00/60.25</td>
<td>2</td>
<td>6.5%</td>
<td>29</td>
</tr>
<tr>
<td>25-OH-vitamin D3 (nmol/l)</td>
<td>55.86 ± 26.09</td>
<td>14.00–114.00</td>
<td>49.00/41.00</td>
<td>22</td>
<td>51.2%</td>
<td>10</td>
</tr>
</tbody>
</table>

IQR: Interquartile range.
OPG: Osteoprotegerin.
RANKL: Receptor activator of nuclear factor-κB ligand.
IL-6: Interleukine-6.
CRP: C-reactive protein.
PTH: Parathormone.

* Normal range varying with regard to gender and menstrual cycle.

Table 5

<table>
<thead>
<tr>
<th>Variable</th>
<th>Correlation with Z-score L1–L4</th>
<th>Correlation with Z-score femoral neck</th>
<th>Correlation with Z-score total hip</th>
</tr>
</thead>
<tbody>
<tr>
<td>r</td>
<td>p-Value</td>
<td>r</td>
<td>p-Value</td>
</tr>
<tr>
<td>BMI</td>
<td>0.360*</td>
<td>0.435*</td>
<td>0.594*</td>
</tr>
<tr>
<td>Duration of depression</td>
<td>0.173</td>
<td>0.173</td>
<td>0.173</td>
</tr>
<tr>
<td>17-Beta estradiol</td>
<td>0.270</td>
<td>0.270</td>
<td>0.270</td>
</tr>
<tr>
<td>RANKL</td>
<td>−0.650*</td>
<td>−0.198</td>
<td>−0.197</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.254</td>
<td>0.131</td>
<td>0.035</td>
</tr>
<tr>
<td>OPG</td>
<td>−0.073</td>
<td>0.017</td>
<td>−0.337</td>
</tr>
<tr>
<td>Osteocalcin</td>
<td>−0.272</td>
<td>−0.270</td>
<td>−0.270</td>
</tr>
<tr>
<td>CrossLaps</td>
<td>−0.166</td>
<td>−0.090</td>
<td>−0.042</td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>0.111</td>
<td>0.094</td>
<td>−0.094</td>
</tr>
<tr>
<td>Hamilton depression score</td>
<td>0.026</td>
<td>0.103</td>
<td>0.555</td>
</tr>
<tr>
<td>IPAQ total</td>
<td>−0.145</td>
<td>−0.256</td>
<td>−0.061</td>
</tr>
</tbody>
</table>

BMI: Body mass index.
BMD: Bone mineral density.
IPAQ: International Physical Activity Questionnaire.
OPG: Osteoprotegerin.
RANKL: Receptor activator of nuclear factor-κB ligand.
IL-6: Interleukine-6.

* p < 0.05.
and had been so for several weeks prior to admission, the results of this questionnaire likely mirror the true amount of activity during the most recent depressive episode quite closely. We found a positive correlation between the level of physical activity and OC levels in our sample, indicating a positive effect of regular exercise on bone, possibly via elevated bone formation.

Interestingly, a large percentage of the patients who were tested showed elevated OPG levels. This is in accordance with findings by Kahl et al. (2006) who found the same results in a subgroup of their sample, consisting of 12 younger depressed women with a mean age of thirty years. The hypothesis that enhanced OPG concentrations may be a compensatory response to enhanced activity of osteoclasts has been established by Ueland et al. (2001). Nevertheless no elevation of the proinflammatory cytokine IL-6, which could have served as a possible source for these elevated OPG concentrations, could be found in our study. RANKL was within normal range in the examined patients, pointing to a state where initially elevated RANKL levels have likely already been counteracted through an elevation of OPG. In another study by Kahl et al. (2005), OPG levels were examined in a sample of young women with MDD, as well as a history of anorexia nervosa. These patients showed a significant decrease in OPG levels and a reduced BMD. One could theorize that in depressive patients with other comorbidities which have a negative impact on bone (such as eating disorders in the cited study), the protective effect of OPG dissolves and BMD decreases.

As OPG has been discussed to play a role in the pathophysiology of mental disorders (Hope et al., 2010), possibly through neurotoxic effects (Jefferson et al., 2007), further studies in patients with MDD should take this parameter into account.

The strengths of our study were both self- and expert-rating on depressive symptoms and the evaluation of physical activity prior to our study. Our study has some limitations: Firstly, the number of patients is quite small, although it should be mentioned that this is the case in many other studies in the field. Secondly, dietary deficiencies were not collected through a questionnaire, but rather through the occurrence of calcium reduction in the blood samples, in cases where no pathological values could be found (data not shown). Still, a reduction of 25OHD in approximately 75% of our patients could point to at least a slight malnutrition, although only two of those patients showed elevated PTH as a possible compensatory mechanism. Also of note is that we investigated some of the patients during the winter months when 25OHD-levels can be lower. Low vitamin D deficiency may play a role in depression. Med Hypotheses 2007:69:1136–1139.

References


