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Treatment of a major depression episode suppresses markers of bone turnover in premenopausal women

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ABSTRACT

Both decrease in bone mineral density and increase in bone turnover had been reported in patients with major depression compared to healthy controls. But the effect of antidepressant treatment on markers of bone turnover is not studied. The aim of this study was to investigate the effect of treatment of a major depressive episode with an SSRI antidepressant on bone turnover in premenopausal women.

Methods: Fifty premenopausal female patients with newly diagnosed major depression according to DSM IV-R criteria were included into the study. Before starting antidepressant therapy (escitalopram 10 mg/day) and three months later, blood samples were collected for the measurement of serum calcium, phosphorus, osteocalcin, β-CTX and iPTH. Depressive status was determined with Hamilton Depression Scale.

Results: Treatment of depression did not create any change in laboratory levels of either calcium or phosphorus. Basal iPTH level was significantly decreased with the treatment. Treatment resulted in an increase in serum osteocalcin and decrease in β-CTX levels. HAMD score was significantly correlated with both osteocalcin and β-CTX. The decrease in β-CTX and increase in osteocalcin levels were more prominent in patients with a HAMD score that remained below 15 than above 15 at the end of the study period. In conclusion, this study shows that with the treatment of depression bone formation increases and bone resorption decreases in premenopausal women with major depression.

1. Objective

Major depression is the most common psychiatric disorder in primary care settings and is seen in 9.6% of adults (Serrano-Blanco et al., 2010) and women are affected 2.7-fold more than men (Gabilondo et al., 2010). It is an important health problem since all cause mortality is increased in major depression with a hazard ratio of 3:1 for men and 1:7 for women (Zheng et al., 1997). It has also been found to be associated with functional disability (Wells et al., 1989) and increased risk of falls (Whooley et al., 1999; Cesari et al., 2002). Additionally, many studies link depression to increased risk of fractures (Whooley et al., 1999; Søgaard et al., 2005). Bone mineral density was found to be decreased both in women and men with major depression (Schweiger et al., 2000; Michelson et al., 1996). Besides, women with osteoporosis have significantly higher levels of depressive symptoms and a corresponding higher prevalence of depression, independent of other factors strongly associated with osteoporosis, such as age or body mass index (Coelho et al., 1999).

Diverse pathophysiological mechanisms have been postulated to explain the development of osteoporosis in major depression. Markers of bone turnover, major determinants of osteoporosis, have been found to be increased and is related to low bone mineral density in patients with major depression (Petronijević et al., 2008; Kahl et al., 2006). The effect of antidepressant treatment on bone is confusing since some population-based studies report an increase in the risk of fractures with the use of SSRI group antidepressants in elderly patients with depression in both sexes (Ziere et al., 2008; Richards et al., 2007; Haney et al., 2007). On the other hand, they do not provide information about younger patients and pathophysiological mechanisms such as bone turnover are not studied. The aim of this study was to investigate the effect of treatment of a major depressive episode with an SSRI antidepressant on bone turnover in premenopausal women.

Abbrevations used: DSM-IV, Diagnostic and statistical manual of mental Disorders-IV; β-CTX, The carboxy-terminal cross-linking telopeptide of type I collagen, beta-CrossLaps; iPTH, Intact parathormone; HAMD, Hamilton Depression scale.

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2. Materials and methods

2.1. Subjects

Fifty consecutive premenopausal women, age 18–45 years with newly diagnosed major depression were included into the study. Three of the patients either withdrew their consent or did not return back to follow-up visits during study period. Forty-seven patients finished the total study. Major depression was diagnosed according to DSM-IV-R diagnostic criteria (American Psychiatric Association, 2000).

Patients were selected from the mood disorder clinic of psychiatry department of Yeditepe University Hospital from January 2008 to December 2008. A total of 80 patients were screened and 50 of them fulfilling the inclusion criteria were admitted into the study. Major reasons for exclusion were patients either being in climacteric or postmenopausal period or coexisting disorder that can affect bone metabolism. Patients were selected after a psychiatric assessment and diagnosis of major depressive disorder according to DSM-IV-R by a psychiatrist. No structured clinical interview such as Structured Clinical Interview for DSM Disorders (SCID) was used. Patients in their first depressive episodes were selected in order to be homogenous. Subjects with history or evidence of any chronic systemic or bone disease, pregnancy or a history of heavy smoking, drug, or alcohol abuse were excluded. Patients taking or on treatment with any drug that affect bone metabolism or any psychiatric medication over a 3-month period prior to the start of study were also not included. None of the subjects in the study group used antidepressant drugs before. All subjects were regularly menstruating. Each subject was screened by clinical history, thorough physical examination, and routine chemical analysis for the evidence of any disease.

This study was conducted in accordance with the guidelines proposed in the Declaration of Helsinki and was approved by the local ethical committee of our university hospital. All subjects gave informed consent before the study began.

2.2. Study design

After recruitment of the subjects, blood samples in vacutainer tubes were obtained between 08:00–09:00 A.M. after an overnight fast before starting antidepressant medication and at the end of study period (3 months). Blood samples were immediately cold centrifuged and stored at −80 °C until analysis. Anthropometric measurements of body weight, height and BMI were also recorded. Escitalopram at a dosage of 10 mg/day was instituted to all patients in study group and followed-up four weeks apart by the psychiatrist with clinical variables for the response. If the response was not satisfying, the dosage was increased to 20 mg/day at week 4. Study was conducted to be ended at the third month irrespective of the depressive status. After that period, patients were followed-up according to the protocols of psychiatry clinic and treatment was continued in patients who required further therapy. Depression status was assessed with Hamilton Depression Scale before starting antidepressant drug and at the end of study period. Scores between 0 and 6 indicate a normal person with regard to depression, scores between 7 and 17 indicate mild depression, scores between 18 and 24 indicate moderate depression, and scores over 24 indicate severe depression (Hamilton, 1960).

2.3. Assays

2.3.1. β-Crosslaps (β-CTX)

Morning fasting serum samples were collected and stored at −80 °C. All samples were studied at the same time with electrochemiluminescence immunoassay (ECLIA) (β-Crosslaps/serum, COBAS, Roche Diagnostics GmBH, Mannheim). Intra and interassay coefficients of variation were 4.7% and 7.6%, respectively.

2.3.2. Osteocalcin

Blood samples were collected into vacutainer tubes in the morning after an overnight fasting and the serum obtained was stored at −80 °C. All samples were studied at the same time. Plasma osteocalcin was measured with a commercial electrochemiluminescence immunoassay kit (N-MID Osteocalcin, COBAS Roche Diagnostics GmBH, Mannheim). Intra- and interassay coefficients of variation were 1.6% and 6.5%, respectively.

2.3.3. Intact parathormone

iPTH levels were determined in plasma samples obtained from EDTA containing vacutainer tubes with electrochemiluminescence immunoassay (PTH, COBAS Roche Diagnostics GmBH, Mannheim). Intra- and interassay coefficients of variation were 6.5% and 3.4%, respectively.

2.3.4. Calcium and phosphorus

Serum calcium and phosphorus was measured with spectrophotometry using commercial kits (Calcium and Phosphate (Inorganic) ver.2 COBAS INTEGRA 400/700/800 Roche Diagnostics GmBH, Mannheim). Serum samples were obtained from vacutainer tubes. Intra- and interassay coefficients of variation for serum calcium and phosphorus were 0.9% and 1.5%, 1.0% and 1.7%, respectively.

2.4. Statistical analysis

Statistical data were analyzed by the SPSS 15.0 for Windows. Data were subjected to normality test (Kolmogorov–Smirnov) and determined to be normally distributed. Parametric tests were used for the analysis. Descriptive statistics were presented as mean ± SD. Paired data for the change in each parameter during study period were analyzed with paired *t* test. To test whether patients' response levels differ in bone turnover markers, we further divided patient group into two: responders and partial responders. Paired data in each group were analyzed by paired *t* test and differences between groups with unpaired *t* test. Pearson test was used for the correlation analysis. Two-tailed *p* values less than 0.05 were taken as significant.

3. Results

Demographic characteristics of the subjects were as follows: mean age of patients was 30 ± 5 years and mean BMI was 24.9 ± 2.4 kg/m^2. There was no difference in history of parity. None of the patients had history of alcohol abuse, heavy smoking or any fracture. Moderate history of smoking with less than 10 per day was

Table 1
Laboratory findings of study subjects.

	Patients ($n = 47$)	
	Basal	End
Calcium (mg/dl)	9.36 ± 0.55[a]	9.20 ± 0.43
Phosphorus (mg/dl)	3.30 ± 0.55[a]	3.41 ± 0.51
iPTH (pg/ml)	48.63 ± 13.70[b]	43.15 ± 14.8[b]
Osteocalcin (ng/ml)	20.66 ± 3.99[b]	23.47 ± 3.96[b]
β-CTX (ng/ml)	0.31 ± 0.13[c]	0.23 ± 0.10[c]

Values are mean ± SD.
[a] $p < 0.05$.
[b] $p < 0.01$.
[c] $p < 0.001$.