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Bone Density Characteristics and Major Depressive Disorder in Adolescents

Pouneh K. Fazeli, MD[a], **Nara Mendes, BA**[a], **Melissa Russell, MD**[a], **David B. Herzog, MD**[b], **Anne Klibanski, MD**[a], and **Madhusmita Misra, MD, MPH**[a,c]

[a]Neuroendocrine Unit, Massachusetts General Hospital and Harvard Medical School, 55 Fruit Street Boston, MA 02114

[b]Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, 55 Fruit Street Boston, MA 02114

[c]MassGeneral Hospital for Children, Massachusetts General Hospital and Harvard Medical School, 55 Fruit Street Boston, MA 02114

Abstract

Objective—Major depressive disorder (MDD) is common during adolescence, a time period characterized by rapid bone mineral accrual. MDD has recently been associated with lower bone mineral density in adults. Our objective was to determine whether MDD is associated with bone mineral density (BMD), bone turnover markers, vitamin D and gonadal steroids in adolescents.

Methods—Sixty five adolescents 12 to 18 years of age (32 boys: 16 with MDD and 16 controls, and 33 girls: 17 with MDD and 16 controls) were included in a cross-sectional study. BMD and body composition were obtained by dual energy x-ray absorptiometry. Estradiol, testosterone, 25-OH vitamin D levels and P1NP, a marker of bone formation, and CTX, a marker of bone resorption, were measured.

Results—Boys with MDD had significantly lower BMD at the hip (Mean [SD] of 0.99 [0.17] vs. 1.04 [0.18] g/cm^2; BMI-adjusted p=0.005) and femoral neck (0.92 [0.17] vs. 0.94 [0.17] g/cm^2; adjusted; BMI-adjusted p=0.024) compared to healthy controls after adjusting for BMI. This significant finding was maintained after also adjusting for lean mass and bone age (hip: p=0.007; femoral neck: p=0.020). In girls, there were no significant differences in BMD between the girls with MDD and the controls after adjusting for BMI (p-values>.17).

Conclusions—Male adolescents with MDD have significantly lower BMD as compared to healthy controls after adjusting for body mass and maturity. This association is not observed in girls.

Keywords

Bone mineral density; adolescents; depression

INTRODUCTION

Major depressive disorder (MDD) is a common disorder among adolescents (1). The prevalence is approximately two to three percent among school age, pre-teen children and

Address for Correspondence: Madhusmita Misra, MD, MPH, BUL 457, Neuroendocrine Unit, Massachusetts General Hospital, 55 Fruit Street, Boston, MA, 02114, P: 617-726-3870; F: 617-726-8528; mmisra@partners.org.

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increases to four to eight percent in teenagers (2, 3). Adolescence is also a critical time for the accrual of bone mass, and more than 90% of peak bone mass is acquired by 18 years. Whereas recent studies have demonstrated a relationship between MDD and lower BMD in adults, this relationship has not yet been fully defined in adolescents. Although a number of studies examining the relationship between BMD and depression have been inconsistent, three recent meta-analyses report that the weight of the evidence supports the statement that patients with MDD have lower BMD compared with controls (4–6). The etiology of this decreased BMD in individuals with MDD is likely multifactorial and includes decreased physical activity and have poor dietary habits as compared to those without MDD (7, 8). Importantly, medications used to treat MDD, especially serotonin reuptake inhibitors (SSRIs), have also been associated with bone loss (9, 10) and increased fracture risk (11).

MDD is associated with an increased risk of obesity (12–14). A prospective study of 9375 seventh through twelfth graders found that non-obese participants with baseline depression (n~753) had an increased risk of obesity after 12 months of follow-up (15). A history of childhood depression has also been shown to be positively associated with adult BMI (16). Whereas obesity was once thought to confer a protective effect on bone because obese individuals have higher BMD than controls, this higher BMD does not persist after adjusting for lean body mass or total body mass. In pre-pubertal children, fat mass has been shown to be inversely associated with both cortical and trabecular density (17). Additionally, visceral adiposity has been shown to be inversely associated with BMD and therefore may be a risk factor for decreased BMD (18). Therefore there are many potential etiologies for the negative association between BMD and MDD.

Given the inverse association between MDD and BMD in adults, we investigated this relationship in male and female adolescents with MDD. We hypothesized that adolescents with MDD would have lower bone mineral density as compared to healthy controls and that bone density parameters would be inversely associated with the severity of the depression.

METHODS

Participants

We recruited 65 participants (32 boys and 33 girls) between September 2007 and December 2009. The participants were between the ages of 12–18 years and had a body mass index (BMI) between the 5^{th} and 95^{th} percentiles for age. Participants with MDD (16 boys and 17 girls) were referred by local psychiatrists. Healthy control participants (16 boys and 16 girls) were recruited from outpatient pediatric practices and outpatient health care centers affiliated with the Massachusetts General Hospital for Children (from which these adolescents received their routine health evaluations) by using mass mailings and fliers. Adolescents with a medical condition or who were taking medications that could affect bone metabolism (including estrogen/progesterone or glucocorticoids) within the preceding 3 months were excluded. Adolescents with any other axis I disorder except for co-morbid anxiety were also excluded, as were those with suicidal ideation. The Partners HealthCare institutional review board approved this study and informed written consent and assent were obtained from all parents and participants.

Experimental Protocol

All participants had a history and physical exam performed and blood was drawn for laboratory studies at our Clinical Translational Science Center. Menstruating girls were evaluated during the first ten days of the follicular phase of the menstrual cycle. Physical activity scores were assessed using the Modifiable Activity Questionnaire (19). Participants were also evaluated by a study psychiatrist to verify the diagnosis of MDD and to assess

their safety for study participation. Participants completed the Children's Depression Inventory (CDI) questionnaire (20) and Children's Depression Rating Scale – Revised (CDRS-R) questionnaire (21) as a self-report of depressive symptoms. A bone age x-ray of the left hand and wrist was obtained and assessed using the standards of Greulich and Pyle (22). All participants underwent dual energy x-ray absorptiometry (DXA) to measure BMD of the lumbar spine (L1–L4), hip and body composition including fat mass (kg), lean mass (kg), and percent body fat using a Hologic Discovery A densitometer (Hologic Inc., Waltham, MA). Lumbar spine bone mineral apparent density (BMAD) was calculated using published methods (23). Coefficients of variation of DXA have been reported as <1% for bone (24), 1.1% for lean body mass and 2.7% for fat mass (25).

Biochemical Assays

CTX-1, P1NP, 25-OH vitamin D and IGF-1 were all measured using a chemiluminescence analyzer (IDS-iSYS Immunodiagnostic Systems Inc, Fountain Hills, AZ). CTX-1 had a detection limit of 0.023 ng/mL, an interassay coefficient of variation (CV) of 6.2% and an intra-assay CV of 3.2%. P1NP had a detection limit of 2 ng/mL, an inter-assay CV of 4.6% and an intra-assay CV of 2.9%. 25-OH vitamin D had a detection limit of 5 ng/mL, an inter-assay CV of 12.1% and an intra-assay CV of 8.3%. IGF-1 had a detection limit 10 ng/mL, an inter-assay CV of 5.1% and an intra-assay CV of 2.2%.

Estradiol, testosterone and sex hormone binding globulin (SHBG) were measured using a chemiluminescent immunoassay (Access Immunoassay Systems, Beckman Coulter, Inc, Fullerton, CA). The detection limit for estradiol was 20 pg/mL with a precision of 12–21%. The detection limit for testosterone was 10 ng/mL with an inter-assay CV of 4.2–7.1% and an intra-assay CV of 1.7–3.9%. The detection limit for SHBG was 0.33 nmol/L with an inter-assay CV of 5.2–5.5% and an intra-assay CV of 4.5–4.8%. Salivary cortisol was assessed using liquid chromatography-tandem mass spectrometry (Mayo Medical Laboratories) (detection limit 50 ng/dl).

Statistical Analysis

Statistical analysis was performed using JMP 9 (SAS Institute, Inc., Cary, NC) software. Means and standard deviations are reported. The means were compared using the Student's t-test, or the Wilcoxon test if the data were not normally distributed. A p-value of < 0.05 on a two-tailed test was used to indicate significance. Pearson correlation coefficients, or if the data were non-normal, Spearman's coefficients, were calculated to assess univariate relationships. Interaction terms were also examined to explore sex differences in the association of MDD and BMD. Multivariable analyses were performed using least-squares linear regression to adjust for confounders. In order to control for the possibility of type 1 error, MANOVA was performed with all of the dependent variables considered simultaneously.

RESULTS

Clinical characteristics

The clinical characteristics of the MDD and control participants are summarized in Table 1. Participants with MDD did not differ from healthy controls in age, bone age, or height. Weight and BMI did not differ in boys with MDD compared to controls, whereas girls with MDD had a significantly higher weight and BMI compared to controls. Both boys and girls with MDD had significantly higher fat mass and percent body fat compared to controls (boys: MDD: 21.8 ± 6.3% versus healthy controls: 17.0 ± 6.2%; $p = 0.029$ and girls: MDD: 31.8 ± 5.7%versus healthy controls: 25.9 ± 4.6%; $p = 0.003$). None of the boys with MDD were hypogonadal and none of the girls with MDD were premenarchal. All girls with MDD

except one reported regular menses. There were no differences in the boys (p=0.75) or girls (p=0.63) with respect to salivary cortisol levels between participants with MDD and the controls. Reported activity levels, and history of smoking and substance abuse did not differ between MDD and controls in either gender. Alcohol use was more common in girls with MDD than controls. Nine boys and 12 girls were using SSRIs and four boys and six girls were using atypical antipsychotic medications.

Bone mineral density

In the group as a whole, there were no significant differences in BMD parameters in those with MDD as compared to healthy controls, in an unadjusted analysis (p = 0.49 – 0.89). Z-scores for BMD at the lumbar spine, hip and femoral neck were lower in boys with MDD compared to controls and these differences were statistically significant after adjusting for possible confounders including BMI, lean mass and bone age (Table 2) and when controlling for type 1 error by performing a MANOVA and considering all dependent variables simultaneously (p<0.001). The differences remained statistically significant after also adjusting for history of SSRI use or use of an atypical antipsychotic, or for 25-OH vitamin D levels (data not shown). In contrast, bone mineral density did not differ in girls with MDD compared to controls, even after adjusting for BMI, lean mass and bone age (Table 2), and also SSRI or atypical antipsychotic use, or 25-OH vitamin D. We also compared bone density in girls with MDD from this study with bone density in obese girls without MDD from a different study (18), and found no difference between the groups (data not shown). There were no significant differences in the number of boys with MDD who had Z-scores at any site that were < −1 (p=1.00) or < −2 (p=0.48) as compared to controls. There were also no significant differences in the number of girls with MDD who had Z-scores at any site that were < −1 (p=0.17) or < −2 (p=0.34) as compared to controls.

Unadjusted correlation coefficients between bone mineral density measurements and BMI, lean mass, bone age, estradiol, free androgen index and fat mass for boys are shown in Table 3. As expected, BMI, lean mass, bone age and estradiol levels were positive determinants of BMD.

When controlling for type 1 error by performing MANOVA and considering all dependent variables simultaneously, BMI, lean mass and bone age remained positive determinants of BMD.

There were no significant correlations between bone density parameters and duration since diagnosis of MDD. There were also no significant correlations between severity of depression, as measured by CDI and CDRS-R, and BMD parameters in the groups as a whole (p = 0.17 – 1.00). In boys, after adjusting for BMI, bone density measurements were inversely associated with both the CDI (lumbar spine BMD Z-score: p=0.034; hip Z-score: p=0.022; femoral neck Z-score: p=0.026) and CDRS-R T-scores (hip Z-score: p=0.034 and femoral neck Z-score: p=0.044).

Markers of bone turnover

P1NP, a marker of bone formation, was lower in MDD as compared to controls in both boys and girls, but this difference was only significant in girls (MDD: 86.7 ± 32.3 ng/mL versus healthy controls: 244.5 ± 270.9 ng/mL; p = 0.031). CTX, a marker of bone resorption, trended lower in girls with MDD as compared to controls (MDD: 0.8 ± 0.3 ng/ml versus healthy controls: 1.5 ± 1.1 ng/ml; p = 0.092). After adjusting for BMI, there were no significant differences in P1NP or CTX between MDD and healthy controls in either gender.

In boys, there were no correlations between age of onset of depression, duration of depression, depression questionnaire scores and markers of bone turnover. In girls, there

were no significant associations between markers of bone turnover and duration of depression or age of onset of depression, but there were negative correlations between markers of bone turnover and depression questionnaire scores (CDI and P1NP: r= −0.41; p=0.026; CDRS-R and P1NP: r = −0.59; p = <0.001; CDRS-R and CTX: r = −0.42; p = 0.027).

Hormone Levels

IGF-1, testosterone and estradiol levels did not differ between the groups in either gender (Table 1). Girls with MDD had a significantly higher free androgen index than controls (4.8 ± 3.8 vs 2.2 ± 1.1; p= 0.024), but this difference was not statistically significant after adjusting for BMI (Table 1). In boys, vitamin D levels were not significantly different in MDD compared to controls even after adjusting for BMI. In contrast, vitamin D was significantly higher in girls with MDD as compared to controls (MDD: 33.5 ± 8.1 versus healthy controls: 22.5 ± 8.0 ng/ml; p < 0.001), and this difference remained statistically significant after adjusting for BMI (p = 0.001).

In boys with MDD, both free androgen index and estradiol correlated positively with bone density measures (Table 3). However, we found no associations of IGF-1 or 25-OH vitamin D levels with bone density (data not shown). Even after adding free androgen index or estradiol to a multivariate model that included the diagnostic group, BMI, lean mass and bone age, boys with depression had lower bone density Z-scores at all sites compared with controls. Similarly even after addition of 25-OH vitamin D or IGF-1 to the multivariate model, differences between the groups remained significant for bone density Z-scores at the spine, hip and femoral neck.

In contrast, we found no significant associations between hormones and bone density measures in girls with MDD and controls (data not shown). Differences in BMD Z-scores in girls with MDD versus controls remained not significant even after adjusting for free androgen index, estradiol, IGF-1 or 25-OH vitamin D levels in the multivariate model.

DISCUSSION

We have shown that boys with MDD have significantly lower BMD compared to healthy boys after adjusting for known determinants of BMD, including lean body mass, BMI and bone age. In contrast, BMD in girls with MDD does not differ from controls despite lower levels of bone turnover markers in MDD and inverse associations with the severity of depression, as assessed by the CDI and CDRS-R questionnaires. These findings illustrate the broad effects of MDD on the overall bone health of adolescents.

In adults, the relationship between BMD and depression has been demonstrated in premenopausal women (26, 27), postmenopausal women (28, 29) and men (30, 31), and three recent meta-analyses demonstrate that the weight of the evidence supports this inverse association between BMD and depression (4–6). Importantly, an increased risk of fracture has also been demonstrated in adults with depression, suggesting that the lower BMD may in fact have significant negative consequences (32).

In adolescents, the relationship between bone mineral density and depression has not yet been well defined. Prior studies in adolescent girls have demonstrated an inverse relationship between self-reported depressive symptoms and total body BMD and hip BMD (33, 34). To our knowledge, the association between BMD and depression in adolescent boys has not been previously studied.

Our results are consistent with gender specific effects of depression on BMD. In adults, evidence also exists to suggest such an effect. Mussolino et al studied the relationship between depression and BMD in young adults (ages 20–39 years) from the Third National Health and Nutrition Examination Survey (NHANES III) and found that both major depression and dysthymia were associated with lower BMD in males but not in females (31). Gonadal status of the participants was not reported in this study. Similarly, Halbreich *et al* studied medicated individuals with MDD, schizophrenia or affective disorder and found that while both males and females had BMD values significantly lower as compared to age and sex-matched normative data, males were more significantly affected as compared to female patients (35). In contrast, Robbins *et al* studied males and females ≥ 65 years of age and found that depressive symptoms were inversely associated with total hip BMD in Caucasian females but not males (29). Therefore, while in younger age groups depressive symptoms appear to affect males more significantly than females, in older aged groups, females appear to be more significantly affected as compared to males.

The cause of lower BMD in adults and adolescents with depressive symptoms is likely multifactorial. Individuals with depressive symptoms have higher cortisol levels as compared to those without depressive symptoms and cortisol has been shown to be a potential mediator of decreased BMD in adult women with depression (36). Borderline personality disorder, which has also been associated with hypercortisolemia (37), has been shown to be associated with even lower bone mineral density in premenopausal women with comorbid depression as compared to patients with depression alone (38). Poor eating habits (7) and less active lifestyles (8) are also common in individuals with depression, and diet and exercise are critical factors in maintaining bone mass. Importantly, obesity has known negative effects on bone and has been shown to be associated with depression in adolescents and adults (12–14). In particular, visceral fat is inversely associated with BMD in obese adolescents (18). Fintini et al have also shown that obesity has a more negative effect on BMD in obese pubertal boys as compared to girls (39).

Lastly, medications used to treat depression have recently been shown to have detrimental effects on bone. SSRIs have been associated with both bone loss (9, 10) and an increased fracture risk (11, 40). A known side effect of atypical antipsychotics, which are also often used to treat depression, is hyperprolactinemia, which leads to suppression of the hypothalamic-pituitary-gonadal axis and resultant hypogonadism in both males and females. Atypical antipsychotics have been associated with decreased BMD in premenopausal and postmenopausal women (41, 42). However, none of the participants with MDD in this study were hypogonadal and adjusting for a history of SSRI and/or atypical antipsychotic use did not change the significant differences in BMD between boys with MDD and healthy controls. Anti-convulsants such as phenytoin and carbamezapine, also occasionally used to treat depression, have negative effects on vitamin D metabolism. These drugs increase metabolism of calcidiol into inactive vitamin D metabolites and phenytoin has been associated with decreased BMD in females (43). However, vitamin D levels did not differ in boys with MDD versus controls, and, in fact, were higher in girls with MDD than in controls.

In this study, we also found inverse associations between bone turnover markers (markers of collagen synthesis and degradation) and severity of depression in adolescent girls whereas in studies of older adults (> 65 years of age), markers of collagen degradation were found to be elevated in depressed individuals (44). The reason for this difference may be due to differences in bone turnover across the age-spectrum with healthy adolescents being in a state of bone acquisition and therefore a state of increased bone formation and older adults having much higher rates of bone resorption.

Interestingly, in our study, girls with MDD had higher vitamin D levels and a higher free androgen index compared to healthy controls. It is possible that these differential levels masked BMD differences in girls with MDD and controls, although adjusting for vitamin D and free androgen index did not change our findings. Also, our data are consistent with previous studies demonstrating differential effects of depression on males as compared to females. The potential mechanism of this differential effect in males versus females is unknown. Perhaps one of the main mediators of low bone density in depression is obesity and increased visceral fat. As Fintini *et al* demonstrate, obesity has a significant negative effect on BMD in boys but not girls (39).

The limitations of our study include the fact that it is a cross-sectional study and therefore causation cannot be determined. Secondly, the evaluation of the severity of depressive symptoms was based on questionnaires which rely on self-report. We also do not have data concerning the calcium intake of participants in the study, which may affect BMD. Also, although there were *a priori* reasons to examine the relationship between MDD and BMD for boys and girls separately (31), no interactions were found between sex and MDD for any of the BMD measures. Lastly, we did not assess visceral fat and subcutaneous fat in this study, and were thus not able to determine whether differences in regional fat mass affect bone metabolism in MDD.

In conclusion, we have demonstrated that boys with MDD have significantly lower BMD as compared to healthy controls and this effect is not seen in girls with MDD. It is critical for providers caring for adolescents, particularly males with depression, to be aware of this association and the potential for increased risk of fracture. Further studies in adolescents will be important to better delineate this relationship.

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Acronyms

MDD	major depressive disorderl
BMD	bone mineral density
BMAD	bone mineral apparent density
P1NP	N-terminal propeptide of type 1 procollagen
CTX	Type I collagen C-telopeptide
BMI	body mass index
SSRI	selective serotonin reuptake inhibitor
CDI	Children’s Depression Inventory
CDRS-R	Children’s Depression Rating Scale-revised
DXA	dual energy x-ray absorptiometry

IGF-1	Insulin-like growth factor-1
SHBG	sex hormone binding globulin

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Table 1

Clinical characteristics and hormone levels of boys (left) and girls (right) with major depressive disorders (MDD) and healthy controls

	BOYS		p	p**	GIRLS		p	p**	p†
	MDD n=16	Controls n=16			MDD n=17	Controls n=16			
Age (years)	16.8 ± 1.5	16.4 ± 2.0	0.44		16.6 ± 1.4	16.3 ± 2.2	0.69		0.79
Bone Age (years)	16.9 ± 1.6	17 ± 1.9	0.62*		17.0 ± 0.9	16.1 ± 2.0	0.34*		0.25
Height (cm)	176.1 ± 8.5	173.6 ± 8.7	0.41		162.4 ± 4.5	162.9 ± 5.6	0.83		0.41
Weight (kg)	76.8 ± 20.0	67.5 ± 15.9	0.16		64.2 ± 11.0	54.7 ± 9.6	**0.013**		0.97
BMI (kg/m^2)	24.4 ± 4.4	22.2 ± 4.0	0.16		24.3 ± 3.7	20.5 ± 2.7	**0.002**		0.41
Fat mass (kg)	17.7 ± 9.0	12.2 ± 6.5	**0.037***		21.3 ± 7.3	14.7 ± 5.0	**0.003***		0.75
Lean mass (kg)	58.0 ± 12.3	54.4 ± 10.5	0.38		42.3 ± 4.5	39.1 ± 5.6	0.084		0.92
Years since diagnosis	2.6 ± 2.6	--------			1.9 ± 1.2	--------			0.34
% of MDD subjects with history of SSRI use	56%	--------			71%	--------			0.41
% of MDD subjects with history of atypical antipsychotic use	25%	--------			35%	--------			0.54
History of smoking	40%	12.5%	0.11		6%	0%	0.48		0.99
History of alcohol use	42.9%	18.8%	0.24		41.2%	0%	**0.007**		0.99
History of other substance abuse	35.7%	18.8%	0.42		11.8%	0%	0.48		0.99
Any fracture after 10 years	31.3%	18.8%	0.69		11.8%	6.3%	1.00		0.99
CTX (ng/mL)	0.8 ± 0.3	1.8 ± 1.1	0.86	0.42	1.8 ± 1.0	1.5 ± 1.1	0.092*	0.54	0.14
PINP (ng/mL)	249.9 ± 188.6	324.6 ± 272.2	0.64*	0.79	86.7 ± 32.3	244.5 ± 270.9	**0.031***	0.51	0.45
IGF-1 (ng/mL)	307.9 ± 75.1	320.2 ± 79	0.65	0.62	294.4 ± 67.9	318.8 ± 97.9	0.43	0.92	0.77
25-OH vitamin D (ng/mL)	28.3 ± 8.2	31.3 ± 9.0	0.47*	0.42	33.5 ± 8.1	22.5 ± 8.0	**<0.001**	**0.001**	**0.002**
Estradiol (pg/mL)	26.5 ± 16.2	22.2 ± 7.6	0.34	0.60	94.4 ± 112.9	130.4 ± 120.5	0.40*	0.60	0.34
Testosterone (ng/dL)	503.6 ± 115.8	395.1 ± 209.2	0.087	0.17	40.9 ± 20.4	31.2 ± 14.7	0.27*	0.96	0.12
SHBG (nmol/L)	28.3 ± 13.7	29.2 ± 15.5	0.90*	0.52	54.0 ± 51.4	49.6 ± 10.6	0.15*	0.43	0.71
Free Androgen Index	80.7 ± 36.7	60.9 ± 37.4	0.15	0.40	4.8 ± 3.8	2.2 ± 1.1	**0.024**	0.82	0.20
Salivary Cortisol (ng/dL)	81.0 ± 54.7	91.6 ± 91.6	0.75*	0.54	51.7 ± 4.8	50.6 ± 2.0	0.63*	0.52	0.70

Mean ± SD

*Wilcoxon test used to analyze between group differences;

** p value after controlling for BMI

† p-values for MDD x gender interaction term

SHBG: sex hormone binding globulin

Table 2

Bone mineral density measures in boys (left) and girls (right) with major depressive disorders (MDD) and healthy controls

	BOYS						GIRLS					
	MDD (n=16)	**Controls (n=16)**	**p**	**p***	**p****	**p*****	**MDD (n=17)**	**Controls (n=16)**	**p**	**p***	**p****	**p*****
Lumbar spine BMD (g/cm^2)	0.95 ± 0.18	0.96 ± 0.17	0.86	0.11	0.14	0.18	0.95 ± 0.12	0.92 ± 0.15	0.47	0.36	0.67	0.46
Lumbar spine BMD Z-score	− 0.26 ± 1.20	0.07 ± 1.06	0.41	**0.025**	**0.035**	**0.024**	− 0.51 ± 1.31	− 0.59 ± 1.02	0.85	0.17	0.27	0.32
Lumbar spine BMAD (g/cm^2)	0.13 ± 0.02	0.14 ± 0.02	0.49	**0.056**	0.079	0.11	0.14 ± 0.02	0.14 ± 0.02	0.63	0.33	0.51	0.38
Hip BMD (g/cm^2)	0.99 ± 0.17	1.04 ± 0.18	0.49	**0.005**	**0.005**	**0.007**	0.92 ± 0.10	0.90± 0.12	0.56	0.33	0.54	0.49
Hip BMD Z-score	− 0.29 ± 1.27	0.19 ± 1.28	0.30	**0.004**	**0.005**	**0.006**	− 0.24 ± 0.93	− 0.32 ± 0.99	0.80	0.31	0.48	0.55
Femoral Neck BMD (g/cm^2)	0.92 ± 0.17	0.94 ± 0.17	0.64	**0.024**	**0.015**	**0.020**	0.84 ± 0.12	0.83 ± 0.12	0.77	0.23	0.37	0.36
Femoral Neck BMD Z-score	− 0.15 ± 1.26	0.15 ± 1.23	0.49	**0.006**	**0.007**	**0.010**	− 0.47 ± 1.06	− 0.41 ± 0.93	0.86	0.19	0.26	0.32

Mean ± SD

*p-value after controlling for BMI;

**p-value after controlling for BMI and lean mass;

***p-value after controlling for BMI, lean mass and bone age;

p-values for the MDD x gender interaction term were non-significant for all bone density parameters

BMD: bone mineral density; BMAD: bone mineral apparent density

Table 3

Univariate analyses in boys of bone density measures with body composition parameters, bone age, hormone levels and depression severity scores (using the CDI and CDRS-R T-scores)

	BMI		Lean mass		Fat mass*		Bone age*		Free androgen index		Estradiol*		CDI*		CDRS-R*	
	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p
Lumbar spine BMD	**0.67**	**< 0.001**	**0.84**	**< 0.001**	0.27	0.14	**0.44**	**0.012**	**0.58**	**< 0.001**	**0.58**	**< 0.001**	0.23	0.22	0.01	0.95
Lumbar spine BMD Z-score	**0.61**	**< 0.001**	**0.63**	**< 0.001**	**0.38**	**0.032**	0.12	0.53	**0.46**	**0.011**	**0.51**	**0.003**	0.13	0.50	−0.07	0.71
Lumbar spine BMAD	**0.57**	**< 0.001**	**0.68**	**< 0.001**	0.12	0.51	**0.47**	**0.007**	**0.52**	**0.003**	**0.54**	**0.001**	0.08	0.68	−0.10	0.60
Lumbar spine BMAD Z-score	**0.55**	**0.001**	**0.59**	**< 0.001**	0.18	0.32	0.28	0.13	**0.49**	**0.006**	**0.58**	**< 0.001**	0.11	0.57	−0.09	0.64
Hip BMD	**0.71**	**< 0.001**	**0.85**	**< 0.001**	**0.36**	**0.043**	**0.51**	**0.003**	**0.54**	**0.002**	**0.53**	**0.002**	0.11	0.55	−0.07	0.71
Hip Z-score	**0.67**	**< 0.001**	**0.72**	**< 0.001**	**0.43**	**0.014**	0.29	0.11	**0.51**	**0.004**	**0.52**	**0.002**	0.15	0.44	−0.07	0.70
Femoral Neck BMD	**0.72**	**< 0.001**	**0.86**	**< 0.001**	**0.36**	**0.042**	**0.52**	**0.003**	**0.58**	**< 0.001**	**0.56**	**< 0.001**	0.22	0.24	0.01	0.95
Femoral Neck BMD Z-score	**0.74**	**< 0.001**	**0.80**	**< 0.001**	**0.50**	**0.004**	**0.40**	**0.025**	**0.57**	**< 0.001**	**0.58**	**< 0.001**	0.19	0.31	−0.002	0.99

*Spearman's rho used to assess correlations

Significant associations are in bold

BMD: bone mineral density; BMAD: bone mineral apparent density