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THE EFFECT OF ANTIPSYCHOTICS ON BONE MINERAL DENSITY AND SEX HORMONES IN MALE PATIENTS WITH SCHIZOPHRENIA

Süheyla Doğan Bulut[1], Serdar Bulut[2], Dicle Görkem Atalan[1], Rıza Gökçer Tulaci[1], Türker Türker[3], Eda Gürçay[4] & Çiğdem Aydemir[5]

[1]*Dışkapı Yıldırım Beyazıt Teaching and Research Hospital, Department of Psychiatry, Ankara, Turkey*
[2]*Yenimahalle Teaching and Research Hospital, Department of Psychiatry, Ankara, Turkey*
[3]*Gülhane Military Medical School, Public Health Department, Ankara, Turkey*
[4]*Dışkapı Yıldırım Beyazıt Teaching and Research Hospital, Physical Medicine and Rehabilitation Department, Ankara, Turkey*
[5]*Numune Teaching and Research Hospital, Department of Psychiatry, Ankara, Turkey*

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SUMMARY

Background: *The aim of this study was to compare the bone mineral density (BMD) of male schizophrenia patients with those of healthy controls in order to determine the relationship between BMD and hormonal changes.*

Subjects and methods: *The study sample included male outpatients between 18 and 55 years old, diagnosed with schizophrenia who had used prolactin-raising antipsychotics (n=23) and prolactin-sparing antipsychotics (n=19) for at least twelve months, along with an age– matched healthy control group. A socio-demographic form was administered, BMD and T-score measurements were performed with a DEXA test, and hormone levels were measured with commercial test kits.*

Results: *The prolactin levels of the prolactin-raising group (PRG) were significantly higher than those of the healthy control group (CG) and the prolactin-sparing group (PSG). While prolactin levels were normal in the CG, hyperprolactinemia was found in 15.8% (n=3) of patients in the PSG and 65.2% (n=15) of subjects in the PRG. Estradiol levels for the PRG and PSG were similar but significantly lower than those of the CG. There was a statistically significant difference between the PRG, PSG and CG in terms of their L1-4 total actual bone density and T-scores. BMD and T-scores were lower for the PRG in comparison with the PSG and CG, and were consistent with osteopenia. Although not observed for every tested region, a negative correlation was found between age, duration of therapy, duration of illness, and T-scores. A positive correlation was found between subjects BMI and T-scores. A consistent negative correlation was found between total testosterone and L1-4 total T-scores when corrected according to prolactin and estradiol. A linear regression analysis found significant relationships between age, BMI, duration of therapy, duration of illness, chlorpromazine equivalent dose, estradiol and testosterone affected T-scores for some regions.*

Conclusions: *The long-term use of prolactin – raising antipsychotic medications as well as hyperprolactinemia and hypoestrogenism accelerate bone degradation.*

Key words: *schizophrenia - bone mineral density – antipsychotics - osteoporosis*

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INTRODUCTION

Schizophrenia is a severe and chronic-relapsing disorder that is associated with marked functional impairments (Kane et al. 2010). Many health problems like cardiovascular diseases, obesity, metabolic syndrome, dental problems, sexual problems and osteoporosis may accompany schizophrenia at higher rates than those found in the general population (Hert et al. 2011, 2012). Osteoporosis is one of the damaging health problems but associated mortality and morbidity rates can be decreased by taking precautions. Patients with schizophrenia may be at risk for osteoporosis because of limited physical activity, smoking, alcohol consumption, malnutrition and insufficient exposure to sunlight. But in addition to these factors, recent studies have also shown that antipsychotic medications may cause bone degradation (Javaid & Holt 2008).

Antipsychotic medications block the inhibiting effect of dopamine on prolactin by blocking dopamine D2 (DA2) receptors in the tuberoinfindubulary system. This can cause hyperprolactinemia (Haddad & Wieck 2004). In clinical practice, hyperprolactinemia is defined as a plasma prolactin level of >20 ng/mL for men and >25 ng/mL for women (Freeman et al. 2000). The DA2 antagonist effects of some atypical antipsychotics such as olanzapine, clozapine and quetiapine are not long lasting and they do not cause long–term hyperprolactinemia. These antipsychotics with a limited effect on prolactin are called prolactin-sparing antipsychotics. Those with long-term prolactin release with a potent DA2 antagonist effect are called prolactin-raising antipsychotics. Conventional antipsychotic medications, risperidone, paliperidone and amisulpiride are among the antipsychotics included in this group (O'Keane & Meaney 2005).

High prolactin levels suppress the secretion of pulsatile gonadotropine – releasing hormone (GnRH) from the hypothalamus and result in hypogondotropic hypogonadism. The secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland also decreases with the suppression of GnRH secretions from the hypothalamus. With decreases in those hormones, secretions of estradiol, testosterone and progesterone also decrease (Dickson et al. 1999). Estrogen is a well-known and prominent factor in bone metabolism. Hypoestrogenism leads to an increased risk for osteoporosis. Estrogen inhibits osteoclastic activity while increasing gene expression in osteoblasts and increasing levels of type I collagen produced by osteoblast cells. Estrogen also affects the synthesis of 25-hydroxyvitamin D and the absorption of calcium in the intestine. There are few studies of testosterone's relationship to bone metabolism. However, due to its effect on osteoblastic activity, low levels of testosterone are correlated with osteopenia and/or osteoporosis (Bridges et al. 1990). On the other hand, hyperprolactinemia may directly affect bone turnover by stimulating bone reabsorption relative to bone formation (Goffin et al. 2002, Seriwatanachai et al. 2008, Motyl et al. 2012).

The aim of this study was to compare the BMD of patients diagnosed with schizophrenia and treated with prolactin-raising and prolactin-sparing neuroleptics with those of healthy controls and to examine the relationship between BMD and hormonal changes in patients with schizophrenia.

SUBJECTS AND METHODS

Subjects

This study included 42 male outpatients aged 18 to 55 diagnosed with schizophrenia according to DSM-IV-TR diagnostic criteria (American Psychiatric Association 2000) along with 39 age matched control subjects determined to have no major psychopathology.

Patients with schizophrenia and control subjects found to have any disease known to cause osteoporosis (endocrinologic, bone diseases, etc) or who used medications that might cause osteoporosis (glucocorticoids, heparine, lithium, anticonvulsants and antityroids) were excluded from the study. All schizophrenia diagnosed subjects had used a single antipsychotic medication (olanzapine, risperidone, quetiapine or haloperidol) for at least twelve months and were in partial or full remission. Antipsychotic medications were used at a therapeutic dose range and there were no other dose limitations.

This study was approved by the local ethic committee. All subjects provided written informed consent for participation in the study after the study procedure had been fully explained.

Socio-demographic data form was administered to participants who met the study criteria to obtain information on height, weight, age, smoking history, physical activity, diet, marital status, duration of illness, duration of antipsychotic use and antipsychotic dosage. The dosages of antipsychotics used by the patients were calculated in terms of chlorpromazine equivalent doses (Woods 2003) and the antipsychotic medication dosages used were compared based upon those chlorpromazine equivalent dosages. Physical activity was categorized as 4 or more times a week, 1-3 times a week and less than 1 time a week. Patients with a body mass index (BMI) below 18.5 kg/m2 were categorized as underweight, 18.5–24.9 kg/m2 were categorized as normal, those weighing 25.0–29.9 kg/m2 were categorized as overweight, and those at 30 kg/m2 or more were categorized as obese according to WHO classifications (WHO, Expert Consultation 2004). Haloperidol (n=14) and risperidone (n=9) are considered prolactin-raising antipsychotics and olanzapine (n=11) and quetiapine (n=8) are considered prolactin- sparing antipsychotics.

The hormone levels and BMD of the prolactin-raising group (PRG), prolactin-sparing group (PSG) and of the healthy control group (HCG) were compared.

Biochemical assessment

Serum levels of FSH, LH and testosterone were measured by the chemiluminescence immunoassay method using a DXI 800 (Beckman-Coulter) hormone analyzer. Plasma estradiol and prolactin levels were determined with a commercially available immunassay kit produced by Modular Analytics E 170 (Elecsys module) system.

Venous blood samples for patients enrolled in this study were drawn between 08:00-10:00 AM, placed in anticoagulant tubes and then serum was separated by centrifugation for 10 min 3000 rpm/ min. Sera was stored at -80°C. When the complete series of patient samples had been collected, sera were studied all at one time in a hormone laboratory. For males, prolactin levels of 2.5-18ng/mL, estradiol levels of 11-44pg/mL, FSH levels of 1.3-13.6 mIU/ mL, LH levels of 1.2-10 mIU/mL and testosterone levels of 2.4-9.5 mg/ mL were considered within normal limits.

Assessment of Bone Mineral Density

Bone mineral density was measured with dual energy X-ray absorptiometry (DEXA) in the lumbar spine (L1-L4) and in the femoral neck, trochanter and Ward's area regions of the proximal right femur. According to World Health Organization guidelines, a T-score ≥-1.0 represents normal bone mineral density. Osteopenia is defined as a T-score between -1.0 and -2.5, and osteoporosis is defined as T-scores ≤-2.5 (World Health Organization. 1994).

Statistical analyses

Statistical analyses were performed using SPSS software version 22.0 (SPSS, Chicago, IL). Descriptive analyses were presented using frequencies, percentages, means, and standard deviations. Continuous variables were investigated with a Kolmogorov–Smirnov test to determine normal distribution. A chi-square test was used to compare categorical variables in different groups. A Student's t-test, one-way analysis of variance, Kruskal-Wallis test or Mann-Whitney U were used to compare continuous variables between the study groups. Multivariable linear regression analyses with BMD as a dependent variable were performed to identify the determinants for BMD. The results of all multiple linear regression analyses were expressed as β coefficients. A p value of <0.05 was considered statistically significant.

RESULTS

Socio-demographic characteristics

The demographic data for all subjects are shown in Table 1. There were no significant differences between the groups in age, physical activity, marital status and diet. However, there were significant differences between the groups in smoking habits and BMI. The difference identified for smoking was found to be related to differences between the CG and the PRG (Mann Whitney U test with Bonferroni correction, p<0.001). The BMI of the CG was significantly lower than those of the PRG and PSG (Mann Whitney U test with Bonferroni correction, p values <0.006 and <0.015, respectively). While there was a statistically significant difference between the PRG and PSG in terms of antipsychotic use duration, no differences could be found between duration of illness and chlorpromazine equivalent dosages (See Table 1).

Hormonal assessment

The hormonal data of the patient groups included in the study is given in Table 2. While there was no statistically significant difference between the PRG, PSG and CG in terms of FSH and testosterone levels, there was a statistically significant difference between their LH, prolactin and estradiol levels (See Table 2). Estradiol levels of the PRG and PSG were significantly lower than those of the control group (Mann Whitney U test with Bonferroni correction, p values 0.045 and <0.001, respectively). The estradiol levels of the PRG and PSG were similar. Prolactin levels for the PRG were significantly higher than those of the CG and the PSG (Mann Whitney U test with Bonferroni correction, p values <0.001 and 0.003, respectively). The LH levels of the PRG were significantly lower than the CG and PSG. There were no significant differences in LH levels between the PSG and the CG.

Table 1. Sociodemographic and clinical characteristics of the groups

	CG (n=39)	PSG (n=19)	PRG (n=23)	p
Age (years) (X±SD)	35.77±10.10	38.95±10.67	37.04±10.28	0.518*
Marital status				
Married	76.9% (30)	42.1% (8)	34.8% (8)	*<0.001***
Single	15.4% (6)	31.6% (6)	60.9% (14)	
Divorced	7.7% (3)	26.3% (5)	4.3% (1)	
Duration of illness (years) (X±SD)	-	8.37±7.12	9.87±9.28	0.751***
Duration of antipsychotic use (month) (X±SD)	-	24.68±16.95	95.65±120.60	*0.001****
Smoking (per day) (X±SD)	7.10±9.35	16.89±16.95	26.09±19.00	*<0.001**
Physical activity				
<once per week	84.6% (33)	53.2% (12)	91.3% (21)	0.103**
1-3 times per week	15.4% (6)	31.6% (6)	8.7% (2)	
≥4 times per week	0% (0)	5.3% (1)	0% (0)	
Diet				
yes	84.6% (33)	89.5% (17)	100% (23)	0.145**
no	15.4% (6)	10.5% (2)	-	
Clorpromazine equivalent dose (mg/day)	-	532.42±373.96	454.34±201.64	0.878***
BMI	22.93±3.82	26.73±3.96	25.91±4.08	*<0.001**

* Kruskal-Wallis test; ** Chi-square test; *** Mann-Whitney U

Table 2. Hormonal characteristics of the groups

	CG (n=39)	PSG (n=19)	PRG (n=23)	p
Prolactin (ng/mL)	6.71±2.82	13.30±12.31	27.62±21.64	*<0.001**
Estradiol (pg/ mL)	26.86±8.29	21.42±10.27	17.47±6.71	*<0.001**
Testosterone (ng/mL)	4.92±1.78	4.65±1.84	5.29±1.92	0.531**
FSH (mIU/ mL)	4.01±2.43	5.02±2.36	5.04±3.23	0.105*
LH (mIU/mL)	4.38±1.68	4.88±2.10	3.44±1.13	*0.018***

* Kruskal-Wallis test; ** One-way ANOVA

All of the control group cases had normal prolactin levels. 15.8% (n=3) of the cases included in the PSG had hyperprolactinemia. Hyperprolactinemia was found in 65.2% (n=15) of the cases in the PRG.

Bone Mineral Density Data

Table 3 shows BMD and T-scores in the lumbar and femoral regions as measured for the control and patient groups. There is a statistically significant difference between the PRG, PSG and CG in terms of L1-4 total actual bone density and L1-4 total T scores. We observed that BMD and T-scores were lower in the PRG as compared with the PSG and CG, and that is consistent with osteopenia (See Table 3). No statistically significant difference was found between the groups in terms of BMD and T scores in the femoral neck, trochanter, ward's and total femur areas (See Table 3).

Correlation and Regression Analysis

A negative correlation was found between age and femoral neck, femoral ward's and femoral total T-scores (r=-0.275, p=0.078; r=-0.387, p=0.011 and r=-0.258, p=0.099, respectively). A positive correlation was found between BMI and lumbar total and femoral total T-scores (r=0.303, p=0.051 and r= 0.400, p=0.009, respectively). A negative correlation was found between the duration of illness and femoral trochanter T-scores (r=-0.291, p=0.061). A negative correlation was found between the duration of antipsychotic use and lumbar total, femoral neck and femoral trochanter T-scores (r=-0.382, p=0.013; r=-0.390, p=0.011 and r=-0.326, p=0.035, respectively). There is a low – degree negative correlation between total testosterone and L1-4 total T-scores (r=0.261, p=0.018). A low-degree negative correlation was also found when the negative correlation between lumbar total T-scores and testosterone levels was corrected with reference to estradiol (r=-0.271, p=0.015) and prolactin (r=-0.264, p=0.018).

Table 4 shows regression analysis results related to factors that may affect the bone areas we tested. We found effects related to lumbar total, duration of therapy (p=0.046, Beta=-0.289), BMI (p=0.029, Beta=-0.312) and estradiol (p=0.048, Beta=-0.281); femoral total, duration of therapy (p=0.005, Beta=-0.397) and BMI (p=0.018, Beta=0.024); femoral neck, age (p=0.002, Beta=-0.587), duration of illness (p=0.022, Beta=0.412), BMI (p=0.009, Beta=0.382), estradiol (p=0.004, Beta=0.385) and total testosterone (p=0.020, Beta=0.359); femoral trochanter, chlorpromazine equivalent dose

Table 3. Lumbar, Femoral BMD and T score in control and patient group

	CG (n=39)	PSG (n=19)	PRG (n=23)	p
Actual bone density (mean ± SD, g/cm2)				
L1-L4 (total)	1.01±0.10	1.02±0.11	0.92±0.11	*0.005**
Femur				
Neck	0.89±0.08	0.88±0.10	0.85±0.10	0.355*
Trochanter	0.73±0.07	0.71±0.07	0.69±0.08	0.187*
Ward's area	0.68±0.32	0.73±0.16	0.70±0.12	0.781*
Femur total	0.96±0.08	0.95±0.08	0.92±0.11	0.452*
T Score (mean ± SD)				
L1-L4 (total)	-0.62±0.95	-0.58±1.05	-1.42±0.97	*0.021**
Femur				
Neck	-0.30±0.70	-0.30±0.78	-0.40±0.69	0.858*
Trochanter	-0.42±0.57	-0.50±0.56	-0.56±0.64	0.652*
Ward's area	-0.22±0.90	-0.38±1.18	-0.56±0.91	0.423*
Femur total	-0.42±0.57	-0.52±0.60	-0.71±0.78	0.241*

*One-way ANOVA

Table 4. Linear regression analyses of variables affecting T-Score at the lumbar region

Variables	Lumbar total (R^2=0.318)		Femoral total (R^2=0.303)		Femoral Neck (R^2=0.485)		Femoral Trochanter (R^2=0.420)		Femoral Ward's (R^2=0.151)	
	β	p	β	p	β	p	β	p	β	p
Age	NS	NS	NS	NS	-0.587	0.002	-0.369	0.055	-0.389	0.011
Duration of Therapy	-0.289	0.046	-0.397	0.005	NS	NS	NS	NS	NS	NS
Duration of Illness	NS	NS	NS	NS	0.412	0.022	0.371	0.067	NS	NS
Chlorpromazine Equivalent Dose	NS	NS	NS	NS	NS	NS	-0.341	0.026	NS	NS
Diet	NS	NS	NS	NS	-0.229	0.082	-0.262	0.066	NS	NS
BMI	0.312	0.029	0.024	0.018	0.382	0.009	0.568	0.001	NS	NS
Estradiol	0.281	0.048	NS	NS	0.385	0.004	0.301	0.033	NS	NS
Testosterone	NS	NS	NS	NS	0.359	0.020	0.435	0.011	NS	NS

NS: nonspecific

(p=0.026, Beta=-0.341), BMI (p=0.001, Beta=0.568), estradiol (p=0.033, Beta=0.301) and total testosterone (p=0.011, Beta=0.435); and finally between femoral ward's, and age (p=0.011, Beta=-0.389). The determinativeness coefficients (R^2) of the best models we created are as follows: 0.318 for Lumbar total, 0.303 for Femoral total, 0.485 for Femoral neck, 0.420 for Femoral trochanter, and 0.151 for Femoral ward's.

DISCUSSION

Although osteoporosis is considered a women's disease by most clinicians, it is a serious health problem that frequently affects men. While the tendency toward osteoporosis in women increases with menopause as a result of decreases in estrogen, men also face risks for osteoporosis with increasing age associated with decreasing testosterone along with low estrogen levels (Naliato et al. 2005). It has been reported that the probability of a man developing prostate cancer is lower than his probability of suffering from an osteoporotic bone break (Melton 1995).

The risk factors for osteoporosis have been identified as age, sex, medical conditions and use of various medications. Since the relationship of antipsychotics with bone loss is not clear, the World Health Organization (WHO) has not listed antipsychotics among the osteoporosis risk factors. According to the International Osteoporosis Foundation and the National Osteoporosis Foundation of the USA antipsychotics are not included among the medications that cause osteoporosis.

Some studies that examine the relationship between antipsychotic use and bone mineral density in patients with schizophrenia, have reported that antipsychotic use was associated with bone loss (Klibanski et al. 1981, Halbreich et al. 1995, O'Keane & Meaney 2005, Meaney & O'Keane 2007, Rey-Sánchez et al. 2009, Roke et al. 2009). However, others have reported no relationship (Keely et al. 1997, Abraham et al. 2003, Becker et al. 2003, Hummer et al. 2005, Lee et al. 2010, Renn et al. 2010, Sugawara et al. 2011). Many possible reasons have been reported for these studies' varying results. Among the reasons are differences in sample size, the existence or lack of control groups, the selection of samples from among subjects experiencing first psychotic episodes or those with more chronic disorders, and lack of control over other factors that may affect BMD have been cited (Bulut et al. 2014).

Today, it is generally accepted practice to categorize antipsychotics as prolactin – raising and prolactin – sparing depending on their effects on prolactin levels (O'Keane & Meaney 2005, Meaney & O'Keane 2007, Crews & Haves 2012, Bulut et al. 2014). In our study, male patients using antipsychotics were compared with a control group of the same age and gender in terms of lifestyle risk factors (smoking, exercise, nutrition, BMI, etc.) and hormone levels (FSH, LH, prolactin, estradiol and testosterone) known to effect osteoporosis. A limited number of studies in the literature have compared patients with schizophrenia using prolactin-raising and prolactin-sparing antipsychotics along with a control group and have considered other risk factors in addition to hormone parameters. Furthermore, in our study only men were included and this approach eliminates differences between the sexes. No differences between the patient and control groups could be found in relation to nutrition, physical activity and age. BMI was found to be lower in the control group when compared to the other groups, and was found to be similar between the groups using antipsychotics. This sample group is sociodemographically homogeneous except in relation to BMI.

The essential finding of our study is that the lumbar region T-scores and BMD values of patients with schizophrenia in the PRG are low at a statistically significant level. This finding is consistent with other studies that show antipsychotics do effect BMD (O'Keane & Meaney 2005, Meaney & O'Keane 2007, Rey-Sánchez et al. 2009, Roke et al. 2009). No significant effect could be found for femoral region BMD and T-scores. We note that similar results have been reported in the literature (Becker et al. 2003). According to these findings, we can assert that the lumbar region is more sensitive to the side effects of antipsychotic medications than the femoral region and bone loss occurs later in the femoral region.

Among the variables examined in our study, obesity is the only data that is known to be protective against osteoporosis. The average BMI in our PRG group is within the overweight range. In spite of high BMI scores our findings of bone loss in this PRG group makes us think that the risk may be much higher than previously reported.

A study performed recently by Kinon et al. (2013), reported that osteoporosis developed more frequently in male patients with schizophrenia treated with antipsychotics when compared to female patients with schizophrenia similarly treated. In Kinon's study, high prolactin appeared to have caused an increase in bone turnover markers such as osteocalcine in both females and males. But only for men did hypogonadism and low testosterone develop secondary to hyperprolactinemia and cause an increase in bone turnover markers like N-telopeptid. It appears that this dual mechanism caused increased bone degradation in male patients with schizophrenia (Kinon et al. 2013). In our study, no statistically significant difference could be found between the patient and control groups in terms of average testosterone levels. Furthermore, a moderately statistically significant relationship was found between testosterone levels and lumbar total T-scores. This significance persisted even when a correction was made in relation to estradiol and prolactin levels. In other words, a negative correlation was found between testosterone levels and bone loss in regions of degradation. Our

findings are not in accord with the hypothesis stated above that low testosterone levels are linked with increased bone turnover and degradation.

In another study Wang et al. (2014) reported that basal BMD and prolactin levels of patients with schizophrenia who used atypical or conventional antipsychotics and of a control group were similar. In addition, one year later the BMDs of the group using conventional antipsychotics were lower in comparison with those of the atypical antipsychotic use group and control group. In this study the prolactin levels of people using conventional antipsychotics were found to be higher when compared with the patient group that had used atypical antipsychotics. In the conventional antipsychotics patient group, a negative correlation was found between BMD and prolactin levels. Long duration conventional antipsychotic use appeared to have resulted in an increase in prolactin and high prolactin may be an important risk factor for developing osteoporosis (Wang et al. 2014). In our study, there was a significant difference between the PRG, PSG and CG groups in terms of prolactin levels (see table 2). Our male patients with schizophrenia who used prolactin-raising antipsychotics developed hyperprolactinemia, while prolactin was at normal levels in the other two groups. This difference in prolactin levels is also is reflected in the BMD and T-scores and these BMD and T-scores are lower for lumbar total in the PRG when compared with the PSG and CG.

Although estradiol levels were not at hypoestrogenism levels, we can report that in both our antipsychotic-using groups, and especially in the PRG, estradiol and LH levels were low. This finding is consistent with hypogonadism development due to hyperprolactinemia. Our study included a multi linear regression analysis and a linear relationship was found between estradiol levels and lumbar total, femoral neck and femoral trochanter region values. As in our study previous studies have reported high prolactin levels and low estradiol levels in both male and female patients with schizophrenia and have found a relationship between low estradiol levels and bone loss (Smith et al. 2002, Kinon et al. 2003). All these findings are evidence for a relationship between hyperprolactinemia, hypoestrogenism and bone loss.

Our study showed a correlation between the duration of illness and T-scores in some of the bone regions examined. In addition, the linear regression analysis showed that the duration of illness affected T-scores for the femoral neck. These findings indicate that schizophrenia alone may result in bone degradation. Adding antipsychotic therapy and lifestyle risk factors to the normal risks of the disease means that osteoporosis risks to patients may be very serious indeed.

In our study, no correlation could be found between chlorpromazine equivalent doses and T-scores. However, in the linear regression analysis, findings were obtained that showed chlorpromazine equivalent doses could create changes in T-scores for the femoral trochanter region. Some studies (Bilici et al. 2002, Meaney et al. 2004, Meaney & O'Keane 2007) have shown that prolactin levels increased and BMD decreased with increases in medication dosages. This may be related to the degree of D2 receptor blockage (Meaney et al. 2004). Based on this, using antipsychotic medications at the smallest possible effective dose could be an important precaution to protect patients against osteoporosis.

Our study found a negative correlation between the duration of therapy and the lumbar total, femoral neck and femoral trochanter T- scores. Our linear regression analysis showed that the duration of therapy affected both lumbar total and femoral total T- scores. Other studies that examined this variable report increased bone loss associated with increased duration of prolactin-raising antipsychotic treatment (Bilici et al. 2002, Meaney et al. 2004, Wang et al. 2014). Our study supports those findings of increased risk of developing osteoporosis as the duration of therapy increases.

The limitations of our study include our relatively small sample size, a lack of information about previous antipsychotic treatments given to these study subjects before current treatment, and a lack of information on vitamin D, parathormone and bone markers that might also be related to bone loss. The fact that duration of illness is the same in the two groups but duration on antipsychotics is much longer in the prolactin raising group is another limitation in terms of the matching study groups. In the future, prospective and longitudinal studies with a larger sample size including drug-naïve and, if possible, patients with the first episode of schizophrenia will provide an enlightenment to the subject. We also believe future studies should examine other variables that may cause bone loss and follow up on hormone levels and bone markers.

CONCLUSIONS

As a result; usage of the prolactin-raising antipsychotics might accelerate bone degradation. Even if prolactin-sparing antipsychotics less often cause hyperprolactinemia and osteoporosis, facing some complications more often such as weight gain, diabetes mellitus, cardiovascular diseases, and early death with these drugs suggest that we should be very careful in the choice of medication. General principles like measuring the BMD and hormone levels periodically, prescribing the lowest effective dose of the antipsychotics, avoiding polypharmacy in patients with schizophrenia, and including the patients to exercise, smoking cessation and diet programs will be protective against any kind of complication.

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Contribution of individual authors:

Süheyla Doğan Bulut & Çiğdem Aydemir designed the study; *Dicle Görkem Atalan & Süheyla Doğan Bulut* searched the literature; *Serdar Bulut & Türker Türker* analysed the data; *Süheyla Doğan Bulut & Serdar Bulut* interpreted the data; *Gökçer Tulacı, Süheyla Doğan Bulut & Eda Gürçay* administered the data to the participants.

References

1. *Abraham G, Paing WW, Kaminski J, Joseph A, Kohegyi E & Josiassen RC: Effects of elevated serum prolactin on bone mineral density and bone metabolismin female patients with schizophrenia: a prospective study. Am J Psychiatry 2003; 160:1618-20.*
2. *American Psychiatric Association: Diagnostic criteria from DSM-IV-TR. American Psychiatric Pub, 2000.*
3. *Becker D, Liver O, Mester R, Rapoport M, Weizman A & Weiss M: Risperidone, but not olanzapine, decreases bone mineral density in female premenopausal schizophrenia patients. J Clin Psychiatry 2003; 64: 761-7.*
4. *Bilici M, Cakırbay H, Guler M, Tosun M, Ulgen M & Tan U: Classical and atypical neuroleptics, and bone mineral density, in patients with schizophrenia. Int J Neurosci 2002; 112:817-28.*
5. *Bridges RS, Numan M, Ronsheim PM, Mann PE & Lupini CE: Central prolactin infusions stimulate maternal behavior in steroid-treated, nulliparous female rats. Proc Natl Acad Sci 1990; 87:8003-7.*
6. *Bulut SD, Bulut S, Tüzer V, Ak M, Ak E, Kısa C et al.: The Effects of Prolactin-Raising and Prolactin-Sparing Antipsychotics on Prolactin Levels and Bone Mineral Density in Schizophrenic Patients. Archives of Neuropsychiatry 2014; 51:205-10.*
7. *Dickson RA, Seman MV & Corenblum B: Hormonal side effects in women: typical versus atypical antipsychotic treatment. J Clin Psychiatry 1999; 61:10-15.*
8. *Freeman ME, Kanyicska B, Lerant A & Nagy G: Prolactin: structure, function, and regulation of secretion. Physiol Rev 2000; 80:1523-631.*
9. *Goffin V, Binart N, Touraine P & Kelly PA: Prolactin: the new biology of an old hormone. Annu Rev Physiol 2002; 64:47-67.*
10. *Haddad PM & Wieck A: Antipsychotic-induced hyperprolactinaemia. Drugs 2004; 64:2291-314.*
11. *Halbreich U, Rojansky N, Palter S, Hreshchyshyn M, Kreeger J, Bakhai Y et al.: Decreased bone mineral density in medicated psychiatric patients. Psychosom Med 1995; 57:485-91.*
12. *Hert M, Correll CU, Bobes CU, Cetkovıch-Bakmas M, Cohen D, Asai I et al: Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in healthcare. World Psychiatry 2011; 10:52-77.*
13. *Hert M, Detraux J, van Winkel R, Yu W & Correll CU: Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. Nat Rev Endocrinol 2012; 8:114–26.*
14. *Hummer M, Malik P, Gasser RW, Hofer A, Kemmler G & Moncayo Naveda RC: Osteoporosis in patients with schizophrenia. Am J Psychiatry 2005; 162:162-7.*
15. *Javaid MK & Holt RI: Understanding osteoporosis. J Psychopharmacol 2008; 22:38-45.*
16. *Kane JM & Correll CU: Past and present progress in the pharmacologic treatment of schizophrenia. J Clin Psychiatry 2010; 71:1115–24.*
17. *Keely EJ, Reiss JP, Drinkwater DT & Faiman C: Bone mineral density, sex hormones, and long-term use of neuroleptic agents in men. Endocr Pract 1997; 3:209-13.*
18. *Kinon BJ, Gilmore JA, Liu H & Halbreich UM: Prevalence of hyperprolactinemia in schizophrenic patients treated with conventional antipsychotic medications or risperidone. Psychoneuroendocrinology 2003; 28:55-68.*
19. *Klibanski A, Neer RM, Beitins IZ, Ridgway EC, Zervas NT & McArthur JW: Decreased bone density in hyperprolactinemic women N Engl J Med 1980; 303:1511-4.*
20. *Lee TY, Chung MY, Chung HK, Choi JH, Kim TY & So HS: Bone density in chronic schizophrenia with long-term antipsychotic treatment: preliminary study. Psychiatry Investig 2010; 7: 278-84.*
21. *Meaney AM, Smith S, Howes OD, O'Brien M, Murray RM & O'Keane V: Effects of long-term prolactin-raising antipsychotic medication on bone mineral density in patients with schizophrenia. Br J Psychiatry 2004; 184:503-8.*
22. *Meaney AM & O'Keane V: Bone mineral density changes over a year in young females with schizophrenia: relationship to medication and endocrine variables. Schizophr Res 2007; 93:136-43.*
23. *Melton LJ: Epidemiology of fractures. In: Riggs BL & Melton LJ (eds): Osteoporosis: Etiology, Diagnosis and Management, second edition, 225-47. Lippincott-Raven Publishers, Philadelphia, 1995.*
24. *Motyl KJ, Dick-de-Paula I, Maloney AE, Lotinun S, Bornstein S, de Paula FJ et al.: Trabecular bone loss after administration of the second-generation antipsychotic risperidone is independent of weight gain. Bone 2012; 50:490- 8.*
25. *Naliato EC, Farias ML, Braucks GR, Costa FS, Zylberberg D & Violante AH: Prevalence of osteopenia in men with prolactinoma. J Endocrinol Invest 2005; 28:12–7.*
26. *O'Keane V & Meaney AM: Antipsychotic drugs: a new risk factor for osteoporosis in young women with schizophrenia?. J Clin Psychopharmacol 2005; 25:26-31.*
27. *Renn JH, Yang NP & Chou P: Effects of plasma magnesium and prolactin on quantitative ultrasound measurements of heel bone among schizophrenic patients. BMC Musculoskelet Disord 2010; 11: 35.*
28. *Rey-Sánchez P, Lavado-García JM, Canal-Macías ML, Gómez-Zubeldia MA, Roncero-Martín R & Pedrera-Zamorano JD: Ultrasound bone mass in schizophrenic patients on antipsychotic therapy. Hum Psychopharmacol 2009; 24:49–54.*

29. *Roke Y, van Harten PN, Boot AM & Buitelaar JK: Antipsychotic medication in children and adolescents: a descriptive review of the effects on prolactin level and associated side effects. J Child Adolesc Psychopharmacol 2009; 19:403–14.*
30. *Seriwatanachai D, Thongchote K, Charoenphandhu N, Pandaranandaka J, Tudpor K, Teerapornpuntakit J et al.: Prolactin directly enhances bone turnover by raising osteoblast-expressed receptor activator of nuclear factor κB ligand/osteoprotegerin ratio. Bone 2008; 42:535-46.*
31. *Smith S, Wheeler M, Murray R & O'Keane V: The effects of antipsychotic-induced hyperprolactinaemia on the hypothalamic-pituitary-gonadal axis. J Clin Psychopharmacol 2002; 22:109-14.*
32. *Sugawara N, Yasui-Furukori N, Fujii A, Saito M, Sato Y, Nakagami T et al.: No association between bone mass and prolactin levels among patients with schizophrenia. Hum Psychopharmacol 2011; 26:596–601.*
33. *Wang M, Hou R, Jian J, Mi G, Qiu H, Cao B et al: Effects of antipsychotics on bone mineral density and prolactin levels in patients with schizophrenia: a 12-month prospective study. Hum Psychopharmacol 2014; 29:183-9.*
34. *WHO Expert Consultation: Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004; 363:157-63.*
35. *Woods SW: Chlorpromazine equivalent doses for the newer atypical antipsychotics. J Clin Psychiatry 2003; 64:663-7.*
36. *World Health Organization: Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: report of a WHO study group. World Health Organ Tech Rep Ser 1994; 843:1-129.*

Correspondence:
Süheyla Doğan Bulut, MD
Dışkapı Yıldırım Beyazıt Training and Research Hospital
Department of Psychiatry
İrfan Baştuğ caddesi No: 12 Dışkapı-Altındağ, Ankara, Turkey
E-mail: dr_sdbulut@hotmail.com