Original article / *Araştırma*

Bone mineral density in patients treated with antipsychotics

Arzu CENGİZ,[1] Vesile ALTINYAZAR,[2] Burcu Gülün MANOĞLU,[2] Fatih VAHAPOĞLU,[2] Oktay KOCABAŞ,[2] İmran KURT ÖMÜRLÜ,[3] Yakup YÜREKLİ[1]

ABSTRACT

Objective: *The aim of this study was to investigate the effect of prolactin levels, duration of disease, accompanying metabolic syndrome, use of mood stabilizer drugs, smoking and exercise on bone mineral density (BMD) in patients treated with antipsychotics.* ***Methods:*** *Fifty-six patients who had been diagnosed with schizophrenia, forty-one patients who had been diagnosed with schizoaffective disorder and thirty three patients who had been diagnosed with bipolar disorders were included the study. BMD was measured at the lumbar spine and femoral sites using dual energy x-ray absorptiometry (DEXA). Arterial blood pressure, waist circumference, fasting glucose, HDL cholesterol and triglyceride levels of the patients were measured for diagnosis of metabolic syndrome. The age, weight, height, smoking habits, regular physical exercise, additional mood stabilizer drugs administered and blood prolactin levels were recorded.* ***Results:*** *Results of 73 patients were osteopenia or osteoporosis. There was no statistically significant relationship between BMD and plasma prolactin level, using additional mood stabilizer drugs, dose of antipsychotic drugs and metabolic syndrome. There was negative correlation between duration of illness, duration of antipsychotic drug use and BMD of the femoral neck. There was negative correlation between duration of smoking and BMD of femoral intertrochanteric region. Lumbar BMD was significantly higher in patients exercising regularly than those of patients without regular physical exercise.* ***Conclusion:*** *Due to a sedantary lifestyle, prolonged use of antipsychotic drugs and smoking risk of osteoporosis increases in patients with schizophrenia, schizoaffective disorder and bipolar disorder. BMD of these patients should be followed-up with regular intervals.* ***(Anatolian Journal of Psychiatry 2019; 20(2):182-188)***

Keywords: *bone density, schizophrenia, bipolar disorders, osteoporosis*

Antipsikotiklerle tedavi edilen hastalarda kemik mineral yoğunluğu

ÖZ

Amaç: *Bu çalışmanın amacı, antipsikotik ile tedavi edilen hastalarda prolaktin düzeyi, hastalık süresi, eşlik eden metabolik sendrom, duygudurum düzenleyici kullanımı, sigara içme ve egzersizin kemik mineral yoğunluğu üzerine etkisini araştırmaktır.* ***Yöntem:*** *Çalışmaya 56 şizofreni hastası, 41 şizoaffektif bozukluk hastası, 33 bipolar bozukluk hastası alınmıştır. Kemik mineral yoğunluğu (KMY) ölçümü lomber vertebra ve femurdan dual enerji X-ray absorpsiyometri (DEXA) kullanılarak ölçüldü. Metabolik sendrom tanısı için hastaların arteriyal kan basıncı, bel çevresi, açlık kan şekeri, HDL kolesterol ve trigliserid düzeyi ölçümleri yapıldı. Yaş, ağırlık, boy, sigara alışkanlığı, düzenli fiziksel egzersiz alışkanlığı, ek duygudurum düzenleyici kullanımı ve kan prolaktin düzeyleri kayıt edildi.* ***Bulgular:*** *Yetmiş üç hastanın sonucu osteopeni veya osteoporoz idi. KMY ile serum prolaktin düzeyi, ek duygudurum düzenleyici kullanımı, antipsikotik ilaç dozu ve metabolik sendrom arasında istatistiksel olarak anlamlı ilişki yoktu. Hastalık süresi ve antipsikotik ilaç kullanım süresi ile femur boyun KMY arasında negative korelasyon saptandı. Sigara içme süresi ile femur intertorakanterik bölge KMY arasında negatif korelasyon saptandı. Düzenli egzersiz yapan hastalarda lomber KMY yoğunluğu düzenli egzersiz yapmayanlardan anlamlı olarak yüksekti.* ***Sonuç:*** *Sedanter yaşam*

[1] MD, Adnan Menderes University Medical School, Department of Nuclear Medicine; [2] MD, Department of Psychiatry; [3] MD, Department of Biostatistics, Aydın, Turkey
Correspondence address / *Yazışma adresi:*
Arzu CENGİZ, MD, Adnan Menderes University Medical School, Department of Nuclear Medicine, Aydın, Turkey
E-mail: arzukincengiz@gmail.com
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tarzı, uzamış antipsikotik ilaç ve sigara içme şizofreni, şizoaffektif bozukluk ve bipolar bozukluk hastalarında osteoporoz riskini artırmaktadır. Bu hastalarda KMY düzenli aralıklarla izlenmelidir. ***(Anadolu Psikiyatri Derg 2019; 20(2):182-188)***

Anahtar sözcükler: *Kemik yoğunluğu, şizofreni, bipolar bozukluk, osteoporoz*

INTRODUCTION

Low bone mineral density (BMD) and prognosis of osteoporosis as to bone fracture in patients with schizophrenia and bipolar disorder using antipsychotic drugs have gradually been noted in recent years.[1] The mortality risk after major fractures in schizophrenia patients was found to be increased by 54% than controls.[2] The overall pooled prevalence of osteopenia was 40.0% and osteoporosis was 13.2% in a recent meta-analysis on decreased BMD in schizophrenia patients and also same datas getting increase in bipolar disorder.[3,4] The prevalence rates of osteopenia and osteoporosis may differ from ages and genders that women have increased risk than men and also significantly increased risk by age.[5] Other underlying mechanisms beside sage and sex that contribute to the development of osteoporosis include hyperprolactinemia. Studies showed that hyperprolactinemia induced by antipsychotic drugs may reduce bone mineral density (BMD) in patients with schizophrenia and bipolar disorder.[6] But, also there are reports revealing that there is no significant correlation between prolactin levels and BMD in patients under antipsychotic drugs.[7,8] Other risk factors such as immobility, smoking and dietary disability might contribute to the osteoporosis in these patients.[9,10] Mood stabilizer drugs such as lithium and valproate, which are administered additionally in these patients, can increase the risk of osteoporosis by increasing the levels of parathyroid hormone.[11]

Metabolic syndrome (MS) is characterized as having central obesity, dyslipidemia, increased blood pressure and impaired glucose tolerance. The incidence of MS in patients with schizophrenia is much higher than the general population.[12] Although obesity is a predictor for bone mineral loss, reports are conflicting about the relation between BMD and metabolic syndrome.[13-15]

In this prospective study, we evaluated the effect of prolactin levels, duration of disease, dose of antipsychotics, use of mood stabilizer drug, metabolic syndrome, smoking and exercise on BMD in patients with the diagnosis of schizophrenia and bipolar disorder with psychotic features treated with antipsychotics.

METHODS

Subjects

Fifty-six patients who had been diagnosed with schizophrenia, forty-one patients who had been diagnosed with schizoaffective disorder and thirty-three patients who had been diagnosed with bipolar affective disorders with psychotic features according to the DSM-IV-TR (American Psychiatric Association 2000) were included in this study. All 130 patients (54 females and 76 males, mean age 40±12) were being treated with antipsychotic drugs for at least one year. Out of 130 patients, 79 were being used mood stabilizer drugs in addition to antipsychotics.

Patients were excluded from the study if they had taken drugs for any disease that could affect bone metabolism (such as glucocorticoids), or physical or mental conditions (substance abuse/dependence, thyroid or parathyroid diseases, renal function impairment, electrolyte imbalance, bone metabolism diseases, pituitary tumor), if their physical activity was limited because of another disease such as stroke or dementia and/or if female patients had been diagnosed with pregnancy, lactation or menopause.

A patients' chart was prepared from all subjects and the following information was noted; age, gender, height, weight, duration of psychiatric treatment, prescription of antipsychotic drugs, smoking habits, age at the onset of illness, exercise habits (the number of times per week) and medical history of other diagnosed diseases. Regular physical exercise was defined as a minimum duration of 30 minutes a day, three days per week. If exercise is less than three days per week and/or shorter than 30 minutes a day it defined as irregular physical exercise.

The grouping of antipsychotics was divided as prolactin raising (PR) and prolactin sparing (PS). Patients receiving first-generation antipsychotic, risperidone, paliperidone, amisulpride or ziprasidone were identified as PR group. Clozapine, olanzapine, quetiapine, or aripiprazole was defined as the PS group and those with both PR and PS antipsychotics were defined as a combination group. Chlorpromazine equivalent antipsychotic doses were used for correlation between BMD and antipsychotic doses.

The Ethics Committee of our hospital approved this study and written informed consent was taken from all patients.

Clinical and biochemical evaluation

Blood samples were obtained from all patients and prolactin levels were measured. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Arterial blood pressure, waist circumference, fasting glucose, HDL cholesterol, triglyceride levels of the patients were measured for diagnosis of metabolic syndrome. If patients had 3 or more of the following criteria, they were supposed to have MS: abdominal obesity (waist circumference ≥90 cm for men and ≥80 cm for women), triglyceride levels were ≥150 mg/dL, HDL cholesterol levels <40 mg/dL for men and <50 mg/dL for women, fasting glucose levels were ≥100mg/dL or use of hypoglycemic drugs and elevated blood pressure(≥130 mmHg systolic and ≥85 mmHg diastolic) or drug treatment for hypertension.[16]

Bone mineral density measurement

BMD was measured at lumbar spine L1-L4, the femoral neck, the trochanteric and intertrochanteric regions of the left hip using dual energy X-ray absorptiometry (DEXA; Hologic Discovery). Osteoporosis was defined if T score -2.5 or lower and osteopenia was defined if T score less than -1 and greater than -2.5 according to the criteria by the World Health Organization guidelines.[17]

Statistical analysis

Descriptive statistics were presented as mean± standard deviations. Compliance with the normal distribution of quantitative variables was evaluated with Kolmogorov Smirnov test. Independent samples T-test and univariate (ANOVA) analysis were used for comparisons between groups which the variables were distributed normally. Mann-Whitney U test and Kruskal Wallis test were used to evaluate the groups which the variables were not distributed normally. Correlation analysis of BMD with other variables was performed by using Pearson's correlation analyses. All statistical analyses were performed with SPSS software version 18.0 and statistical significance was defined as $p<0.05$.

RESULTS

In the present study, the majority of demographic data were similar in the patients of schizophrenia, schizoaffective disorder and bipolar affective disorder with psychotic features except gender. Detailed demographic data of patients shown at Table 1. Clinical and biochemical results and klorpromazine equivalent antipsychotic doses of patients were similar between groups except HDL levels and shown at Table 2.

BMD measurements of 57 patients (43%) were within the normal range, osteopenic in 45 patients (35%) and osteoporosis was diagnosed in 28 patients (22%) according to T-score values in lumbar region. There was no statistically signi-

Table 1. Demographic data of patients with schizophrenia, schizoaffective disorder and bipolar affective disorder with psychotic features

	Schizophrenia (n=56)		Schizoaffective dis. (n=41)		Bipolar disorder (n=33)		
	n	%	n	%	n	%	p
Age (Mean±SD)	41.91±12.70		38.10±9.86		40.30±14.65		0.332
Gender							<0.001
Men	37	66.1	30	73.2	9	27.3	
Women	19	33.9	11	26.8	24	72.7	
Education (Mean±SD, y)	7.46±3.84		8.68±4.28		6.55±3.10		0.061
Marital status							0.602
Single	26	46.4	23	56.1	13	39.4	
Married	21	37.5	12	29.3	18	54.5	
Divorced	9	16.1	6	14.6	2	6.1	
Vocation							0.213
Working	9	16.1	4	9.7	3	9.1	
Workless	17	30.3	22	53.7	14	42.4	
Housewife	21	37.5	8	19.5	16	48.5	
Retired	9	16.1	7	17.1	0	0	
Smoking (year)	21	18.1	12				0.393

Table 2. Detailed clinical and biochemical results of patients

	Schizophrenia(n=56) Mean±SD	Schizoaffective dis.(n=41) Mean±SD	Bipolar dis.(n=33) Mean±SD	p
Duration of illness (year)	11.51±7.69	10.84±6.03	10.33±5.51	0.792
Duration of treatment (year)	11.04±8.01	10.66±6.04	9.24±4.74	0.596
Antipsychotic doses (klorpromazine equivalent)	272.38±182.54	356.07±264.13	248.70±227.69	0.110
Prolactin (ng/mL)	47.87±34.08	39.96±56.54	46.88±63.36	0.835
Metabolic syndrome (n, %)	23 (47.9%)	16 (43.2%)	10 (35.7%)	0.585
Body mass index	29.71±6.79	30.01±4.16	28.13±6.34	0.359
Fasting glucose (mg/dL)	85.22±18.11	82.24±19.63	85.62±19.38	0.702
Waist circumference (cm)	106.25±16.40	104.05±13.09	100.52±18.14	0.272
Systolic blood pressure (mmHg)	126.51±15	122.33±13.19	120.21±12.56	0.076
Diastolic blood pressure (mmHg)	84.94±12.48	84.13±9.57	81.42±10.92	0.360
Triglyceride (mg/dL)	166.02±85.08	171.87±109.07	127.28±64.77	0.099
HDL mg(dL)	43.96±10.86	38.11±10.39	47.97±7.04	<0.001

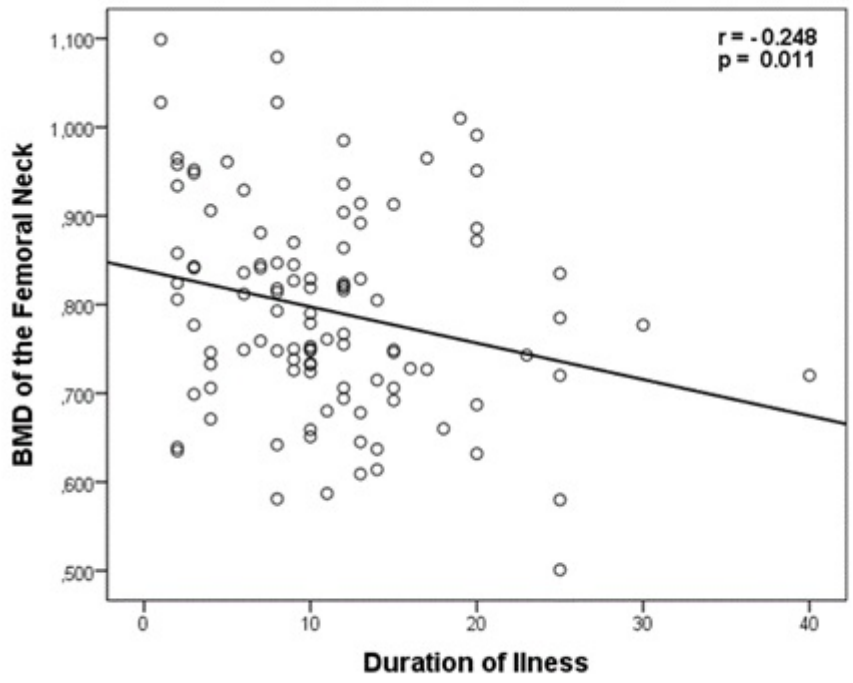

Figure 1. Bone mineral density (BMD) exhibited a negative correlations with duration of illness

ficant difference between BMD in terms of gender or diagnosis of schizophrenia, schizoaffective disorders or bipolar affective disorder.

When correlation analyses were performed, age showed a negative correlation with both lumbar and femoral region BMD and BMI showed positive correlation with lumbar region BMD. Duration of illness and duration of antipsychotic treatment exhibited a negative correlation with femoral neck BMD (Figure 1 and 2). Blood prolactin levels did not show any correlation with any bone region BMD. Dose of antipsychotic drugs were not correlated with BMD. Although BMDs of patients who smoke were not different from those of patients who do not smoke, negative correlation was found between duration of smoking and BMD of femoral intertrochanteric region. Detailed statistical results are shown at Table 3.

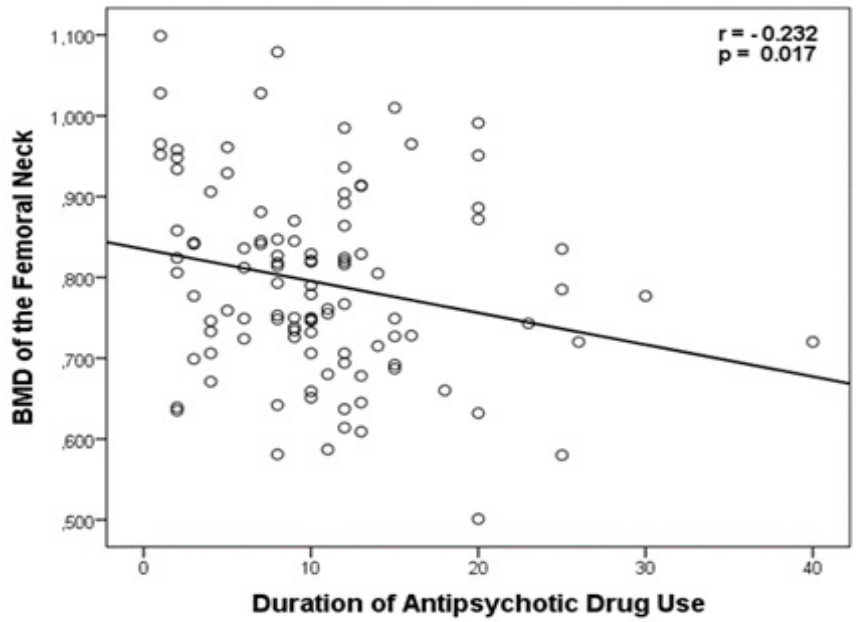

Figure 2. Bone mineral density (BMD) showed a negative correlations with duration of antipsychotic drug use

Table 3. Results of Pearson's correlation coefficients

	L1	L2	L3	L4	Throch.	Intertroch.	Neck
Age	-0.326**	-0.407**	-0.384**	-0.336**	-0.243**	-0.046	-0.447**
BMI	0.219*	0.198*	0.233**	0.183*	0.142	0.167	0.135
Duration of AP treatment	-0.062	-0.181	-0.152	-0.085	-0.041	-0.061	-0.248*
Duration of illness	-0.090	-0.193*	-0.159	-0.072	0.032	-0.022	-0.240*
Doses of antipsychotics	0.112	0.071	-0.003	-0.007	0.007	0.048	0.012
PRL	-0.166	-0.178	-0.076	-0.049	-0.118	-0.220	-0.032
Smoking (year)	-0.109	-0.159	-0.081	-0.041	-0.174	-0.262*	-0.153

**: p<0.05; **: p<0.01;* L1: Lumbar 1; L2: Lumbar 2; L3: Lumbar 3; L4: Lumbar 4; Femoral neck of left hip, trochanteric (throch.) and intertrochanteric (intertroch.) region of left hip; BMI: Body Mass Index; AP: Antipsychotic; PRL: Prolactin.

The serum prolactin levels were high in 60 patients (normal range: 2.58-18.12 ng/mL). Prolactin levels were higher in patients using PR antipsychotics (45.55 ng/mL) or PR+PS combination group (56.58 ng/mL) than patients using PS (33.91 ng/mL), but the difference was not statistically significant (p>0.05).

When the BMDs were analyzed in the patients with hyperprolactinemia and in patients with normal prolactin levels, no significant difference was found between two groups. In addition, there was no statistically significant difference between the groups using mood stabilizer drugs and not using (p>0.05).

Out of 42 patients indicated that they exercise regularly. Twenty-two patients indicated that exercising but not regularly and 15 patients with no exercise. According to the total results of 79 patients, lumbar and femoral neck BMDs were significantly higher in patients who exercising regularly than those of patients who never exercise (p<0.05).

We were able to evaluate 113 patients for MS and 49 patients (43%) were suffering from MS. Ten out of 49 were with the diagnosis of bipolar disease and 39 patients were with the diagnosis of schizophrenia or schizoaffective disorder. There was no statistically significant difference between MS and non MS group for BMD (p>0.05).

DISCUSSION

Hyperprolactinemia is a common clinical problem in patients taking antipsychotic medications.[18] Hyperprolactinemia directly inhibits osteoblasts or inhibits the action of follicle stimulating hormone (FSH) and luteinizing hormone (LH) resulting in decrease of estrogen level.[19] There are controversial studies about the relationship between BMD and hyperprolactinemia. In a cohort study, Takahashi et al. reported a negative impact of elevated prolactin due to antipsychotics on BMD.[1] In contrast, Howes et al. reported that there was no correlation between BMD and prolactin levels.[20] In another study, authors found high rates of osteoporosis and osteopenia in patients taking long term antipsychotic drugs and it was related to the dose and duration of the treatment.[21] In addition, use of concomitant mood stabilizer drugs may also contribute to an increased risk of osteoporosis in these patients.[11] In a study Yang et al. suggested that long term treatment with valproate combined with antipsychotics may adversely affect BMD in premenopausal women with bipolar disorder.[4] In our study we found no statistically significant relationship between BMD and plasma prolactin level or additional mood stabilizer drugs. Dose of antipsychotics did not show any correlation with BMD. However, our results indicated that the risk of osteoporosis increases with long duration of disease and antipsychotic medication. The results also suggest that other factors such as smoking, sedentary lifestyle may contribute to osteoporosis in these patients. We found negative correlation between duration of smoking and BMD of femoral intertrochanteric region. In addition, lumbar vertebrae and femoral neck BMD were significantly higher in patients exercising regularly than those of patients who do not exercise. Both smoking and immobility are risk factors for osteoporosis as it is reported in many studies.[22,23]

Patients who had a diagnosis of psychiatric illness have an increased risk of MS. MS is present 8-56% of patients suffering from bipolar disorder and 11-69% of patients with schizophrenia treated with antipsychotics.[12,24] Many risk factors such as female gender, advanced age, long duration of illness and use of antipsychotics may be associated this syndrome. Nowadays, the relationship between MS and osteoporosis are contradictious. In a meta-analysis study, Zhou et al. suggested that effect of the MS on BMD is relatively minor.[25] Some studies commented that low grade inflammation in patients with MS is associated with osteoporosis despite the protective effects of obesity.[26,27] In our study, we found a positive correlation between BMI and lumbar region BMD. However, BMD values were not statistically different in patients with MS and without a diagnosis of MS. Due to the increased risk of MS and osteoporosis, more comprehensive studies are needed in patients treated with antipsychotics.

Our study has some limitations. We could not evaluated biochemical markers and hormone levels (vitamin D, parathyroid hormone, estrogen i.e.) that may affect bone mineralization. In addition, we were unable to do follow-up measures of BMD in patients.

As a conclusion, prolonged duration of the disease and use of antipsychotic medication could be associated with increased risk of osteoporosis in patient with schizophrenia and bipolar disorder. Sedentary lifestyle and smoking contribute to an increased risk of osteoporosis in these patients. Clinicians should consider this situation and BMD measurement should be obtained before starting treatment with antipsychotics and BMD of these patients should be followed-up with regular intervals.

Authors' contributions: *A.C.: literature review, data collection, writing the manuscript; V.A.: study conception and design, data collection, literature review, writing the manuscript; B.G.M.: data collection; F.V.: data collection; O.K.: data collection; İ.K.Ö.: statistical analysis; Y.Y.: interpretation of data, review the manuscript.*

REFERENCES

1. Takahashi *T, Uchida H, John M, Hirano J, Watanabe K, Mimura M, et al. The* impact *of* prolactin-raising antipsychotics *on bone mineral density in patients with schizophrenia: findings from a longitudinal observational cohort. Schizophr Res 2013; 147:383-386.*

2. *Stubbs B, Gaughran F, Mitchell AJ, De Hert M, Farmer R, Soundy A, et al. Schizophrenia and the risk of fractures: a systematic review and comparative meta-analysis. Gen Hosp Psychiatry 2015; 37:126-133.*

3. *Stubbs B, De Hert M, Sepehry AA, Correll CU, Mitchell AJ, Soundy A, et al. A meta-analysis of prevalence estimates and moderators of low bone mass in people with schizophrenia. Acta Psychiatr Scand 2014; 130:470-486.*
4. *Yang J, Joe SH, Lee MS, Ko YH, Jung IK, Kim SH. Effects of long-term combination treatment with valproate and atypical antipsychotics on bone mineral density and bone metabolism in premenopausal patients with bipolar disorder: a preliminary study. Psychiatry Investig 2011; 8(3):256-261.*
5. *Chen CY, Lane HY, Lin CH. effects of antipsychotics on bone mineral density in patients with schizophrenia: gender differences. Clin Psychopharmacol Neurosci 2016; 31;14(3):238-249.*
6. *Crews MP, Howes OD. Is antipsychotic treatment linked to low bone mineral density and osteoporosis? A review of the evidence and the clinical implications. Hum Psychopharmacol 2012; 27:15-23.*
7. *Halbreich U. Osteoporosis, schizophrenia and antipsychotics: the need for a comprehensive multifactorial evaluation. CNS Drugs 2007; 21:641-657.*
8. *Howes OD, Wheeler MJ, Meaney AM, O'Keane V, Fogelman I, Blake G, et al. Bone mineral density and its relationship to prolactin levels in patients taking antipsychotic treatment. J Clin Psychopharmacol 2005; 25:259-261.*
9. *Halbreich U, Palter S. Accelerated osteoporosis in psychiatric patients: possible pathophysiological processes. Schizophr Bull 1996; 22:447-454.*
10. Kavanagh DJ, McGrath J, *Saunders JB, Dore G, Clark D. Substance misuse in patients with schizophrenia: epidemiology and management. Drugs 2002; 62:743-755.*
11. Misra M, *Papakostas GI, Klibanski A. Effects of psychiatric disorders and psychotropic medications on prolactin and bone metabolism. J Clin Psychiatry 2004; 65:1607-1618.*
12. *Malhotra N, Grover S, Chakrabarti S, Kulhara P. Metabolic syndrome in schizophrenia. Indian J Psychol Med 2013; 35:227-240.*
13. *De Laet C, Kanis JA, Odén A, Johanson H, Johnell O, Delmas P, et al. Body mass index as a predictor of fracture risk: a meta-analysis. Osteoporos Int 2005; 16:1330-1338.*
14. *Jankowska EA, Rogucka E, MedraśM. Are general obesity and visceral adiposity in men linked to reduced bone mineral content resulting from normal ageing? A population-based study. Andrologia 2001; 33:384-389.*
15. *Park KK, Kim SJ, Moon ES. Association between bone mineral density and metabolic syndrome in postmenopausal Korean women. Gynecol Obstet Invest 2010; 69:145-152.*
16. Grundy SM, *Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al.* Diagnosis *and* management *of the* metabolic syndrome. *An American Heart Association/National Heart, Lung and Blood Institute Scientific Statement. Executive Summary Cardiol Rev 2005; 13:322-327.*
17. *Wold Health Organization Guidelines for Preclinical Evaluation and Clinical Trials in Osteoporosis. Geneva: WHO, 1998, p.5-6.*
18. Howes OD, Wheeler MJ, *Pilowsky LS, Landau S, Murray RM, Smith S.* Sexual function *and gonadal hormones in patients taking antipsychotic treatment for schizophrenia or schizoaffective disorder. J Clin Psychiatry 2007; 68:361-367.*
19. *Meaney AM, O'Keane V. Prolactin and schizophrenia: clinical consequences of hyperprolactinemia. Life Sci 2002; 71:979-992.*
20. Howes *OD, Wheeler MJ, Meaney AM, O'Keane V, Fogelman I, Blake G, et al.* Bone mineral density *and its relationship to prolactin levels in patients taking antipsychotic treatment. J Clin Psychopharmacol 2005; 25:259-261.*
21. *O'Keane V. Antipsychotic-induced hyperprolactinaemia, hypogonadism and osteoporosis in the treatment of schizophrenia. J Psychopharmacol 2008; 22:70-75.*
22. Kanis JA, *Johnell O, Oden A, Johansson H, De Laet C, Eisman JA, et al.* Smoking *and fracture risk: a meta-analysis. Osteoporos Int 2005; 16155-16162.*
23. *Howe TE, Shea B,* Dawson LJ, *Downie F, Murray A, Ross C, et al.* Exercise *for* preventing *and* treating osteoporosis *in* postmenopausal women. Cochrane Database Syst Rev 2011; *6;(7).*
24. *Babić D, Maslov B, Martinac M, Nikolić K, Uzun S, Kozumplik O. Bipolar disorder and metabolic syndrome: comorbidity or side effects of treatment of bipolar disorder. Psychiatr Danub 2010; 22:75-78.*
25. *Zhou J, Zhang Q, Yuan X, Wang J, Li C, Sheng H, et al. Association between metabolic syndrome and osteoporosis: a meta-analysis. Bone 2013; 57:30-35.*
26. *Jeon YK, Lee JG, Kim SS, Kim BH, Kim SJ, Kim YK, et al. Association between bone mineral density and metabolic syndrome in pre- and postmenopausal women. Endocr J 2011; 58:87-93.*
27. *Nakamura K, Saito T, Kobayashi R, Oshiki R, Oyama M, Nishiwaki T, et al. C-reactive protein predicts incident fracture in community-dwelling elderly Japanese women: the Muramatsu Study. Osteoporos Int 2011;22: 2145-2150.*