The effect of antipsychotics on bone mineral density in bipolar disorder: a case-controlled pilot study

Bipolar bozuklukta antipsikotiklerin kemik mineral yoğunluğu üzerine etkisi: bir vaka-kontrollü pilot çalışma

Özlem Altındağ[1], İrfan Koca[1], Abdurrahman Altındağ[2], Osman Vırıt[2], Mustafa Yılmaz[3], Haluk Savaş[2], Gökay Alpak[2]

[1]Gaziantep University, Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Gaziantep, Turkey
[2]Gaziantep University, Faculty of Medicine, Department of Psychiatry, Gaziantep, Turkey
[3]Gaziantep University, Faculty of Medicine, Department of Nuclear Medicine, Gaziantep, Turkey

Abstract
The purpose of this study was to evaluate the effect of antipsychotics on bone mineral density in bipolar disorder. A total of 44 premenopausal female patients receiving antipsychotic medication for at least 1 year and 43 healthy premenopausal female volunteers were included in the present study. Clinical evaluation was performed via Hamilton Depression Scale and Clinical Global Impression Scale, bone metabolism via serum levels of calcium, phosphorus, parathormone, alkaline phosphatase (ALP), vitamin D and prolactin, while bone mineral density via dual energy X-ray absorptiometry. Bone mineral density scores were determined to be significantly lower, while prolactin, parathormone and ALP levels were significantly higher in the patient group. Comparison of patient group in itself based on patients under atypical antipsychotic vs. atypical antipsychotic + mood stabilizer treatment revealed no significant difference between groups in terms of clinical and biochemical parameters. In conclusion, contrary to what many studies suggest, our findings revealed that atypical antipsychotics offered no advantages over other medications in the development of secondary osteoporosis in patients with bipolar disorder. There was no significant difference between patients receiving atypical antipsychotics and other mood stabilizers in terms of osteoporosis incidence.
Keywords: Antipsychotics; bipolar disorder; bone mineral density; DXA

Özet
Bu çalışmada bipolar bozukluklarda atipik antipsikotiklerin kemik mineral yoğunluğu üzerine etkisini değerlendirmesi amaçlanmıştır. En az 1 yıldır antipsikotik ilaç kullanmakta olan premenopozal 44 kadın hasta ve 43 sağlıklı gönüllü (premenopozal kadın) çalışmaya dahil edildi. Klinik değerlendirme; Hamilton Depresyon Ölçeği ve Klinik Global İzlenim Ölçeği ile, kemik metabolizması; kalsiyum, fosfor, parathormon, serum alkalen fosfotaz (ALP), vitamin D ve prolaktin düzeyleri ile ve kemik mineral yoğunluğu; dual enerji X-ray absorbsiyometri ile değerlendirildi. Hasta grubunda kemik mineral yoğunluğu skorlarında istatistiksel olarak anlamlı düzeyde düşüklük ve prolaktin, parathormon ve ALP düzeylerinde ise anlamlı düzeyde yükseklik tespit edildi. Hasta grubu kendi içinde, atipik antipsikotik ya da atipik antipsikotik + duygu durum düzenleyici alanlar şeklinde karşılaştırıldığında ise; aynı parametrelerde anlamlı farklılık saptanmadı. Çalışmamızın sonuçları atipik antipsikotiklerin bipolar hastalarda, duygu durum düzenleyicilerden bağımsız olarak sekonder osteoporoz gelişiminde rol oynayabileceğini göstermiştir. Ancak atipik antipsikotiklerin tek başlarına veya duygu durum düzenleyicilerle kombinasyon tedavisi şeklinde kullanıldığında, osteoporoz oluşturma potansiyelleri arasında anlamlı farklılık saptanmadı.
Anahtar kelimeler: Antipsikotikler; bipolar bozukluk; kemik mineral yoğunluğu; DXA

Introduction

Osteoporosis (OP) is a systemic disease characterized by a decrease in bone mass, increase in bone fragility and an increased susceptibility to fractures. OP can place an enormous physical, medical and financial burden on individuals and their families. While the etiopathogenesis has not been clearly defined, its multi-factor origin has been proposed (1,2). The most important risk factor for development of osteoporosis is reduction of gonadal hormone levels. Reduction of gonadal hormone levels is generally related with menopause in women and hypogonadism in men (3). However, it may also occur at a younger age as a complication of certain diseases or medications (glucocorticoids, methotrexate, cyclosporine A, high dose heparin, diuretics, anticonvulsants and antipsychotics, etc.) used in the treatment of these diseases. Being more commonly encountered among young female and males, the incidence of secondary osteoporosis may reach up to 64% particularly in males (4). Several of psychiatric diseases and psychotropic medications have been reported to cause marked chronic or

Correspondence: İrfan Koca, University of Gaziantep, Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Gaziantep, Turkey
Tel:+90 342 3606060/76280 *irfan.koca17@gmail.com*

Received: 10.03.2014 **Accepted:** 09.04.2014
ISSN 2148-3132 (print) ISSN 2148-2926 (online)
www.gaziantepmedicaljournal.com
DOI: 10.5455/GMJ-30-154291

recurrent neuroendocrine alterations besides occurrence or acceleration of the development of osteoporosis (5-8). The negative impact of antipsychotic medications on bone mineral density (BMD) values in schizophrenic patients has been documented in several studies (9). Antipsychotic medications have been proposed to lead a reduction in BMD via decreasing gonadal hormone levels and increasing prolactin levels (9,10). However, BMD is also subject to the influence of various factors such as physical activity, exposure to sunlight and nutrition. These factors with their effect on BMD may have a particular importance in psychiatric disorders given the negative impact of irregular nutrition, insufficient exposure to sunlight and inactivity on peak bone mass in numerous psychiatric diseases. Antipsychotic medications are commonly used in treatment of bipolar disorder, while it is not so simple to decide whether osteoporosis is secondary to underlying disease or due to side effect of the drugs. Data available in literature on the effect of antipsychotic medications on BMD in patients with bipolar disorder are based on limited number of small-scale studies (9-11).

The present study aimed to evaluate BMD and bone metabolism markers in patients receiving antipsychotic or other mood stabilizers with the diagnosis of bipolar disorder.

Materials and Methods

A total of 44 premenopausal female patients presented to psychiatry outpatient clinic between June 2010 and December 2011 while receiving antipsychotic medication for at least 1 year and 43 healthy premenopausal female volunteers were included in the present study. Local ethics committee approval was obtained prior to study. Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study.

Exclusion criteria;

- Poorly nourished or immobilized patients,
- Pregnant or breast-feeding females,
- Those under the age of 18 or those who are in menopause,
- Patients with alcohol or substance abuse or polydipsia,
- Patients with hepatic, renal, thyroid or malabsorptive disorders that may affect bone metabolism
- Patients receiving glucocorticoid, oral contraceptive, vitamin A, thiazide, calcitonin, calcium, or bisphosphonate treatment

The diagnosis of bipolar disorder was made in accordance with Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) diagnostic criteria. Severity of disease was determined via Hamilton Depression Scale, (HAM-D), Young Mania Rating Scale (YMRS) and Clinical Global Impression Scale (CGI-S). After record of data on patient demographics, bone metabolism was evaluated by measurement of serum levels of calcium, phosphorus, parathormone, alkaline phosphatase (ALP), vitamin D and prolactin via routine blood test.

Hamilton Rating Scale for Depression (HAM-D)

The HAM-D was used in its 21-item version (12); it has been widely adopted, has good validity, internal consistency, and inter-rater reliability (12).

Young Mania Rating Scale (YMRS)

The YMRS is a widely used instrument in research and clinical settings for measuring manic symptoms in patients who already have a diagnosis of BD. It is completed by a clinician in a format of a semi-structured interview, which covers predefined anchor points. Questions focus on symptoms of mania: elevated mood, increased motor activity, increased sexual interest, decreased sleep, irritability, pressured speech, thought disorder, abnormal thought content, aggressive behavior, general appearance, and insight. The answers are rated on a scale of 0–4 or 0–8, with higher scores indicating more severe symptoms (13).

Clinical Global Impression (CGI)

This is a well-known assessment tool, usually administered by clinicians in order to evaluate the illness severity (item 1), through the provision of a score between 0 (non-assessed) and 7 (extreme severity). Item 2 assesses the degree of improvement the patient experiences, and item 3 assesses the balance between effectiveness of the treatment provided and importance of side effects. (14).

Bone mineral density measurements were performed via dual energy X-ray absorptiometry (DXA) from two sites including lumbar spine and femur with Ge-Lunar Dpx-Nt Pro (Lunar Corp, Adison, WI, USA) device. T and Z scores of all participants were evaluated according to criteria recommended by International Society Clinical Densitometry (ISCD) 2007 (15).

Statistical analysis

Results are expressed as mean±SD. Analysis of data was made using computer software (SPSS version 16.0, SPSS Inc. Chicago, IL, USA). Intergroup comparison of continuous variables was performed via Student's t-test for normally distributed variables, while with Mann-Whitney U test for non-normally distributed variables.

Results

Age was determined to be 31.8±9.7 (ranged 23-49) years and 36.9±8.4 (ranged 32-48) years in the patient and control groups, respectively. Duration for the disease and related treatment was 51.0±40.0 and 9.2±5.4 months, respectively. In the patient group, HAM-D, YMRS and CGI-S scores were 5.2±3.6, 6.1±2.3 and 1.9±1.1, respectively (Table 1). Of 44 patients

with bipolar disorder, 23 were receiving antipsychotics while 21 were on atypical antipsychotic + mood stabilizer treatment. Mood stabilizers included valproate in 13 patients and lithium in 8 patients.

Total lumbar T scores were -0.7±2.6 and 0.9±0.7, while femur total T scores were 0.2±1.1 and 1.3±0.5 in patients and controls, respectively. Lumbar BMD values were calculated to be 0.9±0.2 and 1.0±0.1, while femur BMD values were 0.9±0.1 and 1.0±0.1 in patient and control groups, respectively. Lumbar and femoral total T-scores as well as BMD values were determined to be significantly lower in patient group compared with control group (P<0.001, for each) (Table 2). Prolactin, parathormone and ALP levels were significantly higher in patients than controls (P<0.001) (Table 2).

Table 1. Demographic characteristics of patients with bipolar disorder and control subjects

	Patients (n=44)	**Controls** (n=43)	**P**
Age (years)	31.8±9.7	36.9±5.3	0.055
Education (years)	6.2±8.3	8.4±7.3	0.062
BMI (kg/cm^2)	29.4±6.1	27.6±6.2	0.082
Duration of disease (months)	51.0±40.0		
Atypical antipsychotic users	23		
Atypical antipsychotic + MS users	21		
Treatment duration (months)	9.2±5.4		
Smoking (yes/no)	9/35	11/32	
YMRS	6.1±2.3		
HAM-D	5.2±3.6		
CGI-S	1.9±1.1		

BMI: Body mass index, MS: Mood stabilizer, YMRS: Young Mania Rating Scale, HAM-D: Hamilton Depression Scale, CGI-S: Clinical Global Impression Scale-Severity of disease

Table 2. Clinical findings in patients with bipolar disorder and control subjects

	Patients n = 43	**Controls n = 41**	**P1**	**Prescribed treatment**		**P2**
				Atypical anti-psychotic	Atypical anti-psychotic + MS	
Lumbar Z score	-0.6±1.1	0.9±2.4	**< 0.001**	-0.6±1.2	-0.6±1.0	0.205
Lumbar T score	-0.7±2.6	0.9±0.7	**< 0.001**	-0.7±2.7	-0.7±2.4	0.109
Femoral Z score	0.2±0.9	1.4±1.7	**< 0.001**	0.2±1.1	0.2±0.7	0.092
Femoral T score	0.2±1.1	1.3±0.5	**< 0.001**	0.2±1.0	0.2±1.3	0.130
Lumbar BMD (g/cm^2)	0.901±0.2	1.022±0.1	**< 0.001**	0.922±0.3	0.883±0.2	0.066
Femoral BMD (g/cm^2)	0.933±0.1	1.043±0.1	**< 0.001**	0.940±0.1	0.924±0.2	0.220
Prolactin *(*ng/ml*)*	57.2±1.2	22.4±0.7	**< 0.001**	58.1±0.9	55.5±1.0	0.072
Parathormone (pg/ml)	90.0±0.8	33.8±1.4	**< 0.001**	88.1±0.8	91.8±0.7	0.088
ALP (IU/l)	183.7±0.8	144.6±0.4	**< 0.001**	180.4±0.9	185.7±0.9	0.102
Calcium (ng/dl)	9.0±0.5	9.3±0.3	0.062	9.0±0.4	9.0±0.5	0.320
Phosphorus (ng/dl)	3.2±0.4	3.2±0.5	0.120	3.3±0.5	3.2±0.6	0.192

BMD: Bone mineral density, ALP: Alkaline phosphatase, MS: Mood stabilizer, P1= Patient (total) vs. control groups. P2=atypical antipsychotic vs. combination treatment groups

Comparison of patient group in itself based on patients under atypical antipsychotic mono-therapy vs. other mood stabilizer therapy revealed no significant difference between groups in terms of BMD and bone metabolism markers (P>0.05) (Table 2).

Discussion

Our findings revealed that atypical antipsychotics may have a role in the development of secondary osteoporosis in bipolar disorder.

There are three principal ways for drugs being used in treatment of different diseases to affect bone metabolism: 1) increase in osteoclastic activity and induction of bone turnover; 2) suppression of osteoblastic new bone formation; 3) suppression of normal osteoid mineralization. Additionally, certain biochemical alterations may occur in bone metabolism during this process including hypocalcemia, hypophosphatemia, decrease in serum levels of biologically active vitamin D metabolites and hyperparathyroidism (3). We consider increased levels of parathormone in patient group to have a negative impact on BMD scores.

Amongst the factors associated with increased osteoporosis incidence in psychiatric patients are polydipsia (16), use of antipsychotic medications and related hyperprolactinemia (17), excessive smoking (16), substance and alcohol abuse (18) and limited physical activity (16). In our study, aiming to evaluate the isolated effect of antipsychotics, patients with history of polydipsia, substance or alcohol abuse and immobilization were excluded from the study. Also, smoking rates were similar between patient and control groups. Hyperprolactinemia may have acute and chronic effects both in females and males. BMD and osteoporosis have also been ranked among these effects (19,20). We consider increased levels of prolactin in the antipsychotic medication receiving group to have a role in the development of osteoporosis.

Typical antipsychotic were documented to be associated with hyperprolactinemia and osteoporosis more commonly than atypical antipsychotics in schizophrenia (21). In this regard, our findings are notable based on the indication that development of marked osteoporosis is also likely with use of atypical antipsychotics.

While hyperprolactinemia developing secondary to drug therapy has been accused for the decrease in BMD in general, some authors indicate that the disease itself may have a direct role in the development of osteoporosis (10,22). Occurrence of low BMD in depression has been linked to increase in cortisol and decrease in estrogen levels (23). Also in schizophrenia, negative symptoms were reported to be associated with osteoporosis (24). Only a few studies are evident in the literature concerning the evaluation of BMD in bipolar disorder. In a past study by Yang et al. (11) conducted with 19 premenopausal female without a control group, decrease in BMD was reported in almost half of patients receiving valproate and low dose atypical antipsychotic treatment for bipolar disorder. However, to date, there no studies to conclude whether or not a drug-independent risk of osteoporosis is present in the bipolar disorder. Our findings emphasize the similar negative impact of atypical antipsychotics and other mood stabilizer agents on BMD in the bipolar disorder. Nevertheless, it is yet unknown if bipolar disorder itself contributes to the development of osteoporosis.

There is no guideline considering follow up and treatment of bone metabolism disorders in patients receiving antipsychotic drugs. Informing patients about characteristics and possible side effects of prescribed drugs is as important as life style related factors effective on BMD (4). Follow up for osteoporosis among females in the postmenopausal period is based on measurement of bone mineral density performed approximately once a year. Given the age of onset in bipolar disorder, it seems obvious that osteoporosis dependent fracture risk may occur in this population at a much younger age than in the general population. Prescription of medications for treatment of bipolar disorder with consideration of the risk-benefit ratio for each individual patient and selection of the lowest effective dose of the drug combined with close follow up of patient would be beneficial.

Being diagnosed at early ages, bipolar disorder is a life-long disorder necessitating continuous drug treatment, while antipsychotic drugs used in the treatment may cause osteoporosis. The principal drugs with well-known negative effects on BMD in bipolar disorder are lithium, valproate and haloperidol (9). Our findings are important to show that atypical antipsychotic have negative effects on BMD in patients with bipolar disorder.

The major limitations of the present study are its cross-sectional design, evaluation of the effects of atypical antipsychotics on BMD without making a comparison to typical antipsychotics or with respect to specific effect of each drug on BMD, and the lack of data on serum levels for gonadal hormone, vitamin D and overall markers of bone turnover.

Since generally expected to manifest itself in the postmenopausal period, osteoporosis may be overlooked in young females due to failure to perform a detailed investigation. Osteoporosis is known to cause painful vertebrate and hip fractures resulting in death in one out of every five cases who developed hip fracture, while leaving survivors with severe sequel and disturbed quality of life. In this respect, it seems reasonable to assess patients diagnosed with bipolar disorder and receiving antipsychotic medication in terms of bone mineral density and risk of osteoporosis with administration of treatment when needed.

Larger scale and controlled studies are needed to clarify the adverse effects of such medications being commonly used in treatment of psychiatric diseases.

References

1. Lone EN, Genant HK. Osteoporosis and bone mineral assessment. In: McCarty DJ (eds). Arthritis and Allied Conditions. Philadelphia: Lea and Febiger 1993;133-49.
2. Heaney RP. Pathophysiology of osteoporosis. Endocrinol Metab Clin North Am 1998;27(2):255-65.
3. Rosen CJ. Pathophysiology of osteoporosis. Clin Lab Med 2000;20(3):455-68.
4. Wolinsky-Friedland M. Drug-induced metabolic bone disease. Endocrinol Metab Clin North Am 1995;24(2):395-420.
5. Sato Y, Kondo I, Ishida S, Motooka H, Takayama K, Tomita Y, et al. Decreased bone mass and increased bone turnover with valproate therapy in adults with epilepsy. Neurology 2001;57(3):445-9.
6. Pack AM, Morrell MJ. Adverse effects of antiepileptic drugs on bone structure: epidemiology, mechanisms and therapeutic implications. CNS Drugs 2001;15(8):633-42.
7. Halbreich U, Palter S. Accelerated osteoporosis in psychiatric patients: possible pathophysiological processes. Schizophr Bull 1996;22(3):447-54.
8. Naidoo U, Goff DC, Klibanski A. Hyperprolactinemia and bone mineral density: the potential impact of antipsychotic agents. Psychoneuroendocrinology 2003;28(Suppl 2):97-108.
9. 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(1):15-23.
10. Misra M, Papakostas GI, Klibanski A. Effects of psychiatric disorders and psychotropic medications on prolactin and bone metabolism. J Clin Psychiatry 2004;65(12):1607-18.
11. 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):256-61.
12. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23(1):56-62.
13. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 1978;133(5):429-35.
14. Endicott J, Spitzer RL, Fleiss JL, Cohen J. The global assessment scale. A procedure for measuring overall severity of psychiatric disturbance. Arch Gen Psychiatry 1976;33(6):766-71.
15. Hangartner TN, Warner S, Braillon P, Jankowski L, Shepherd J. The Official Positions of the International Society for Clinical Densitometry: acquisition of dual-energy X-ray absorptiometry body composition and considerations

regarding analysis and repeatability of measures. J Clin Densitom 2013;16(4):520-36.
16. De Leon J, Verghese C, Tracy JI, Josiassen RC, Simpson GM. Polydipsia and water intoxication in psychiatric patients: a review of the epidemiological literature. Biol Psychiatry 1994;35(6):408-19.
17. Ataya K, Mercado A, Kartaginer J, Abbasi A, Moghissi KS. Bone density and reproductive hormones in patients with neuroleptic-induced hyperprolactinemia. Fertil Steril 1988;50(6):876-81.
18. Lindholm J, Steiniche T, Rasmussen E, Thamsborg G, Nielsen IO, Brockstedt-Rasmussen H, et al. Bone disorder in men with chronic alcoholism: a reversible disease? J Clin Endocrinol Metab 1991;73(1):118-24.
19. Byerly M, Suppes T, Tran QV, Baker RA. Clinical implications of antipsychotic-induced hyperprolactinemia in patients with schizophrenia spectrum or bipolar spectrum disorders: recent developments and current perspectives. J Clin Psychopharmacol 2007;27(6):639-61.
20. Kishimoto T, Watanabe K, Shimada N, Makita K, Yagi G, Kashima H. Antipsychotic-induced hyperprolactinemia inhibits the hypothalamo–pituitary–gonadal axis and reduces bone mineral density in male patients with schizophrenia. J Clin Psychiatry 2008;69(3):385-91.
21. Bilici M, Cakirbay 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(7):817-28.
22. 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(5):485-91.
23. Michelson D, Stratakis C, Hill L, Reynolds J, Galliven E, Chrousos G, et al. Bone mineral density in women with depression. N Engl J Med 1996;335(16):1176-81.
24. 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(4):278-84.

How to cite:

Altındağ Ö, Koca İ, Altındağ A, Vırıt O, Yılmaz M, Savaş H, Alpak G. The effect of antipsychotics on bone mineral density in bipolar disorder: a case-controlled pilot study. Gaziantep Med J 2014;20(3):221-225.