

Factors associated with decreased bone mineral density in postmenopausal women with schizophrenia

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Objective: This study examined the risk factors for decreased bone mineral density (BMD) in postmenopausal women with schizophrenia.

Methods: Cluster sampling method was adopted in this large-sample, cross-sectional study. A total of 219 postmenopausal female inpatients with schizophrenia were selected and interviewed in Beijing. The average age of the patients was 60.4 ± 7.0 years. Clinical assessment instruments included the Positive and Negative Syndrome Scale (PANSS) and a questionnaire with detailed general information and disease-related investigations. Laboratory measurements included prolactin (PRL), estradiol, progesterone, thyroid stimulating hormone, FT3, and FT4. BMD testing was performed by dual-energy X-ray absorptiometry.

Results: The prevalence of osteoporosis or osteopenia was 66.2% (n=145). Decreased BMD was associated with age, illness duration, therapeutic dose (equivalent chlorpromazine dose), treatment duration, PANSS-negative scores, body mass index (BMI), daily exercises (min/d), drinking (unit/wk), PRL, and estradiol. Multiple logistic regression analysis revealed that age, treatment duration, PANSS-negative score, BMI, and PRL were significantly associated with decreased BMD.

Conclusion: Prevalence of BMD loss was higher in Chinese postmenopausal women with schizophrenia compared to the normal BMD group. A combination of demographic and clinical factors play important roles in determining decreased BMD, including older age, longer treatment duration, more PANSS-negative scores, higher BMI, and higher PRL level.

Keywords: schizophrenia, bone density, risk factors

Introduction

The risk of medical comorbidities in patients with schizophrenia is significantly higher than that in the general population,¹ and osteoporosis is one of these. Numerous studies have consistently revealed that patients with schizophrenia have significantly lower bone mineral density (BMD) compared with their peers of the same sex in the general population.^{2,3} This issue has approximately doubled the risk of femoral neck fractures in patients with schizophrenia compared with the normal population,^{4,5} as well as increased rates of morbidity and mortality, which place a heavy economic burden on society.

The etiology of decreased BMD in patients with schizophrenia remains obscure. In recent years, the influence of hyperprolactinemia caused by antipsychotic drugs on BMD has continuously gained more attention from researchers. Numerous studies have found that most patients with chronic schizophrenia on long-term antipsychotic medications (especially “prolactin [PRL]-elevating” drugs) revealed a significantly

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increased risk of decreased BMD or osteoporosis.^{6,7} However, other studies have obtained the opposite result,⁸ which implies that there might be some other factors that affect the BMD of patients with schizophrenia. Indeed, since negative symptoms and social functions decline, schizophrenic illness shows numerous unhealthy lifestyle behaviors that can increase the risk of osteoporosis, which include limited exercise, lack of exposure to sunshine, poor nutrition, smoking, and alcoholism.⁹ However, reports on the effects of unhealthy lifestyle on BMD in patients with schizophrenia are very rare. Merely two studies have found that body mass index (BMI) and smoking may be associated with bone loss in patients with schizophrenia.^{6,10}

However, to date, no study has focused on bone loss in patients with schizophrenia in the People's Republic of China, where there are many different sociodemographic situations compared to other countries. Therefore, examining the factors associated with decreased BMD in patients with schizophrenia is of great importance in the People's Republic of China.

The main aim of our study was to explore the related risk factors for decreased BMD in postmenopausal women with schizophrenia.

Methods

Settings and subjects

In this large-sample, cross-sectional study, cluster sampling method was adopted, and subjects were recruited from a group of patients with schizophrenia confined at the Changping District Hospital of Integrated Chinese and Western Medicine, Beijing, since April 2014. Inclusion criteria were as follows: 1) female patients with a diagnosis of schizophrenia according to the *Diagnostic and Statistical Manual of Mental Disorders, fourth edition* diagnostic criteria and 2) all women >52 years old, who were confirmed to be postmenopausal by a gynecologist as having no menstruation for at least 2 years. Exclusion criteria were as follows: 1) patients who are taking any medication known to be risk factors for BMD decline such as antidepressant and anticonvulsant drugs; 2) patients who have medical disorders known to be risk factors for BMD decline such as alcohol dependence and eating disorder; and 3) patients who have a family history of osteoporosis. From the 692 original samples obtained, 219 patients met our inclusion criteria and participated in this study. The mean age of the patients was 60.4 ± 7.0 years.

Clinical assessment

Symptom severity was rated using the Positive and Negative Syndrome Scale (PANSS).¹¹ The questionnaire included detailed information regarding the general information and

disease-related investigations relevant to BMD, including name, age, sex, date of birth, birth place, education, vocation, marital status and address, age of onset, illness duration, previous disease and drug histories, smoking and alcohol history, serum calcium, serum phosphorus, fasting blood glucose, daily exercises, female menstrual history and current drug administration list, and equivalent chlorpromazine (CPZ) dose of current antipsychotic drug,¹² and was completed for each participant.

Laboratory assessments

Venous blood specimens were collected from patients at 7 to 9 am in the next morning, after fasting for 8–12 hours, by specially trained research nurses. The blood sample (5 mL) was centrifuged at 3,000 rpm for 5 minutes after 4 hours of standing at 4°C. Approximately 1.5 mL of serum was subsequently separated and carefully transferred to a disposable cup and then stored at an ultra-low (–80°C) temperature for subsequent analysis. Before the test, the stored serum samples were removed from the –80°C freezer, placed in a 4°C refrigerator to thaw, and the test was finished within 48 hours. On the day of the test, samples were maintained undisturbed at room temperature until the temperature was balanced. All the tests were accomplished in the clinical laboratory of Changping District Hospital of Integrated Chinese and Western Medicine, Beijing. PRL, estradiol (E2), progesterone, thyroid stimulating hormone, free triiodothyronine (FT3), and free thyroxine (FT4) levels were measured using chemiluminescence with an automated chemiluminescence analyzer ADVIA Centaur (Siemens AG, Munich, Germany).

BMD assessment

BMD testing was performed by dual-energy X-ray absorptiometry (GE Healthcare Bio-Sciences Corp., Piscataway, NJ, USA) in the lumbar spine (L1–L4) and femoral neck. Quality assurance was performed before the measurement; all tests were two-tailed and the random error of replication was <1%. The scan image of bone surface density is defined as 1.001 g/cm², and results can be calculated automatically. *T*-score values, which compare BMD with standardized bone mass for ethnic-, sex-, and age-specific groups, were used in the subsequent analysis. Osteoporosis is defined as a BMD value that falls at least 2.5 standard deviation (SD) below these standardized values, and osteopenia is defined as a BMD value that falls 1 SD below normative values. A BMD value higher than –1.0 SD means normal.

Statistical analysis

Data were analyzed with SPSS 17.0 (Statistical Package for Windows), and results are expressed as mean \pm standard

Table 1 Comparison of demographic and clinical characteristics between abnormal and normal BMD groups of patients with schizophrenia

	Abnormal BMD group (n=145)		Normal BMD group (n=74)		Statistics	
	Mean/median	SD/(Q1, Q3)	Mean/median	SD/(Q1, Q3)	T/Z	P-value
Age	62.1	7.2	59.1	5.2	3.49	0.001
Illness duration (years)	30.9	10.3	28.2	9.4	1.88	0.061
Current therapeutic dose (CPZ)	450.0	(359.1, 612.5)	400.0	(272.9, 612.5)	-2.31	0.021
Treatment duration (years)	28.9	10.5	24.1	9.2	3.46	0.001
Total PANSS score	52.2	13.2	51.7	13.8	0.26	0.798
PANSS positive	12.8	4.3	13.5	5.5	-0.98	0.327
PANSS negative	15.2	4.2	11.7	2.8	7.26	0.000
BMI, kg/m ²	23.5	3.8	25.6	4.6	-3.52	0.001
Calcium	2.2	0.1	2.2	0.1	0.11	0.909
Phosphorus	1.1	0.2	1.2	0.2	-1.45	0.149
FBG	4.8	1.2	5.1	1.8	-1.15	0.252
Exercises per week (minutes)	267.6	109.9	310.2	129.9	-2.55	0.012
No of cigarette smoked per day	0	(0, 10)	0	(0, 10)	-0.09	0.928
Drinking (unit/wk)	1.0	(0, 1.0)	0	(0, 1.0)	-2.95	0.003
TSH	2.9	2.2	3.9	5.8	-1.46	0.147
FT3	2.4	0.4	2.3	0.6	1.73	0.085
FT4	1.0	0.8	1.2	1.5	-1.39	0.168
Prolactin	38.2	26.4	20.4	10.2	7.15	0.000
Estradiol	25.5	14.6	31.9	21.3	-2.29	0.024
Progesterone	0.8	1.1	1.1	2.0	-1.28	0.202

Abbreviations: BMD, bone mineral density; SD, standard deviation; CPZ, chlorpromazine; PANSS, Positive and Negative Syndrome Scale; BMI, body mass index; FBG, fasting blood glucose; wk, week; TSH, thyroid stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; T/Z, T-score/Z-score.

deviation. Independent *t*-tests (two-tailed) and rank-sum test were used to identify significant differences between groups, and χ^2 tests were performed to analyze cross-tabulations wherever appropriate. Multiple logistic regression analyses were performed to identify correlations between variables that hypothesized a priori to be correlated with decreased BMD. A *P*-value <0.05 was considered significant.

Ethical considerations

According to the Guideline for Good Clinical Practice of the International Conference on Harmonisation, the research protocol and the informed consent form was approved by Institutional Review Boards of Peking University's Institute of Mental Health. All subjects or their legal guardians provided written consent after understanding the aims of this study and were included in this study.

Results

The prevalence of osteoporosis or osteopenia among the 219 study participants was 66.2% (n=145). *T* scores of the lumbar spine (L1–L4), left femoral neck, and right femoral neck were -0.7 (-1.8, 0.4), -0.9 (-1.7, 0.1), and -0.8 (-1.8, 0), respectively.

Patients with osteoporosis and osteopenia were assigned into the BMD abnormal group, while the remaining patients were assigned into the normal group. Differences in age,

illness duration, therapeutic dose (CPZ), treatment duration, PANSS-negative scores, BMI, daily exercises (min/d), drinking (unit/wk), PRL, and estradiol between the two groups were statistically significant. Details are shown in Table 1. The multiple logistic regression analysis showed that age, treatment duration, therapeutic dose (CPZ), PANSS-negative scores, BMI, exercises per week (minutes), and PRL were significantly associated with decreased BMD. Details are shown in Table 2.

Discussion

Our study revealed that 66.2% of Chinese postmenopausal women with schizophrenia exhibited decreased BMD. This figure is similar to that reported in other Asian countries,¹³ but is significantly higher than that in European countries.⁶

Table 2 Factors associated with abnormal BMD (multiple logistic regression analysis)

Factor	B	SE	Wald test	P-value	Odds ratio	95% CI
Age	0.10	0.03	9.17	0.002	1.11	1.04–1.19
Treatment duration	0.08	0.03	5.87	0.015	1.08	1.02–1.15
PANSS negative	0.29	0.06	26.59	0.000	1.34	1.20–1.50
BMI, kg/m ²	-0.11	0.05	5.16	0.023	0.89	0.81–0.98
Prolactin	0.05	0.01	13.76	0.000	1.05	1.02–1.07

Abbreviations: BMD, bone mineral density; SE, standard error; CI, confidence interval; PANSS, Positive and Negative Syndrome Scale; BMI, body mass index.

A study reported that BMD of postmenopausal female patients decreased faster and the prevalence of decreased BMD was higher in Asian populations, compared to that in Caucasians.¹⁴ This difference might be due to racial differences and other environmental protective factors such as a higher BMI in white women.¹⁵

The present study revealed that decreased BMD in patients with schizophrenia is associated with hyperprolactinemia and lower estradiol, which implies that decreased BMD is associated with hyperprolactinemia caused by antipsychotics, and lower secondary sex hormone levels. This result has been repeatedly demonstrated in animal experiments.^{16,17} However, results of previous clinical studies have been inconsistent.^{6-9,18-20} The reasons may be related to the following factors: first, the sample size of the previous study was small; second, majority of the methods of grouping were too simple, which only divide the current antipsychotic treatment of schizophrenia into “PRL-raising drug group vs PRL-sparing drug group” or “high dose group vs low dose group”; third, almost all studies did not give a clear definition of other psychiatric medications, which may affect BMD (eg, antidepressants and anticonvulsants). The present study used a larger sample, included postmenopausal women with solely schizophrenia, excluded interferences of antidepressant or anticonvulsant drugs, and considered various lifestyles that sufficiently affect BMD.

Furthermore, our study revealed that decreased BMD in patients with schizophrenia is related to the long treatment duration of antipsychotic drugs, which was not reported in previous studies. This might be related to the large sample size and the sole inclusion of postmenopausal women with schizophrenia in this study. This also confirms that antipsychotics can cause decreased BMD, which warns clinicians to notice the risk of antipsychotic drugs in causing decreased BMD and fractures. Recently, two large studies^{21,22} have consistently found that the use of antipsychotic drugs affects the prevalence of fractures, and the treatment duration of antipsychotics was positively correlated with the risk of fracture.

In addition, this study found that BMI is a protective factor in BMD, which is consistent with previous studies.¹¹ Weight is a mechanical load factor, which has different effects in different parts of BMD, reflecting various parts to withstand various mechanical loads. The greater weight of the bones would bear a greater load and have a higher bone density. In addition, negative symptoms are a risk factor for bone density, which is consistent with previous studies.¹⁹ This may be due to the negative symptoms of schizophrenia, which

would more likely lead to lack of exercise, reduction to sun exposure, and calcium and vitamin D deficiency caused by nutritional deficiencies.

Osteoporosis is a kind of disease that causes serious harm to public health. This study found that the prevalence of BMD loss was higher in Chinese postmenopausal women with schizophrenia, compared to the normal BMD group. In addition, a combination of demographic and clinical factors play important roles in determining decreased BMD, including older age, longer treatment duration, more PANSS-negative scores, higher BMI, and higher PRL levels.

These findings suggest that clinical psychiatrists should pay more attention in monitoring BMD in patients with schizophrenia, especially older female patients with long-term medications. In addition, clinical intervention for patients with decreased BMD can be carried out based on the following aspects: 1) the use of drugs causing minimal influence on PRL, so as to avoid hyperprolactinemia that could result in bone loss; 2) enhance the improvement and treatment of negative symptoms of schizophrenia, thereby increasing patient activity, sunlight exposure, and enough calcium and vitamin D intake; 3) reduce malnutrition in patients with schizophrenia caused by lower-than-normal BMI phenomenon, thereby keeping the patient in the normal weight range, which may also have a protective effect on bone loss.

In the present study, despite the larger sample size than the previous study, the impact of unhealthy lifestyles that decrease BMD in schizophrenia and the influence of antipsychotics were fully considered. However, inevitably, there are some methodological shortcomings. This is a cross-sectional study, rather than a prospective study, and only factors that may be associated with decreased BMD in schizophrenia were found, and a causal relationship could not be determined. Large-sample, prospective studies are needed in the future to further confirm the results of this study.

Conclusion

Prevalence of BMD loss was higher in Chinese postmenopausal women with schizophrenia compared to the normal BMD group. A combination of demographic and clinical factors play important roles in determining decreased BMD, including older age, longer treatment duration, more PANSS-negative scores, higher BMI, and higher PRL level.

Disclosure

The authors report no conflicts of interest in this work.

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