Effects of risperidone on gonadal hormone and bone mineral density in schizophrenia patients

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Objective: Schizophrenia patients have risk for bone mineral density (BMD) loss and osteoporosis. This study aimed to explore the relationship between serum levels of gonadal hormone and bone mineral density or osteoporosis in schizophrenia patients treated with risperidone.

Methods: A total of 250 inpatients with schizophrenia and 288 healthy controls were recruited in present study. BMD of the calcaneus was measured in all participants by the 3.01 Sahara Clinical Bone Sonometer (Hologic). Serum fasting levels of gonadal hormone (prolactin, estradiol, testosterone, progesterone, follicle-stimulating hormone, luteinizing hormone) were analyzed in the patients.

Results: Our results showed that schizophrenia patients had markedly lower BMD levels and higher prevalence of osteoporosis (24.4% vs. 10.1%) compared to normal controls (both $P < 0.001$). Patients with osteoporosis were older, had longer disease courses, higher current smoking rate and lower body mass index (BMI) compared to patients without osteoporosis (all $P < 0.05$). As for gonadal hormone, we found significantly higher prolactin but lower estradiol levels in patients with osteoporosis than those without osteoporosis even confounding variables were controlled (both $P < 0.05$). Correlation analysis demonstrated significant correlation between BMD and the following parameters in the patient group: age, total disease courses, the daily dosage of risperidone, prolactin and estradiol levels (Bonferroni corrected P's < 0.05). Moreover, stepwise multiple logistic regression analysis indicated that the total disease courses, smoking, prolactin and estradiol were responsible for the occurrence of osteoporosis in schizophrenia patients.

Conclusion: Our results suggest a high prevalence of osteoporosis and significant reduced BMD in schizophrenia patients with risperidone monotherapy. The aberrant gonadal hormone levels, especially increased prolactin and reduced estradiol levels were significant related with osteoporosis in those patients.

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Abstract

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Conclusion: Our results suggest a high prevalence of osteoporosis and significant reduced BMD in schizophrenia patients with risperidone monotherapy. The aberrant gonadal hormone levels, especially increased prolactin and reduced estradiol levels were significant related with osteoporosis in those patients.

Keywords: schizophrenia; risperidone; gonadal hormone; osteoporosis; bone mineral density.

1. Introduction

Osteoporosis is a degenerative disease characterized by the decrease of bone mineral density (BMD) and related with high risk for fractures[1]. Epidemiologic data have convincingly indicated that osteoporosis affecting about 200 million people around the world and resulting in increased morbidity and mortality, thus, becoming a major public health issue in the worldwide[2]. Ample studies conducted to explore risk factors for osteoporosis, including old age, female gender, insufficient calcium intake, inadequate physical activity, excessive smoking, excessive drinking, the use of antipsychotics and so on[3, 4].

Schizophrenia is a severe, chronic and debilitating disorder that affects around 1% of the population in the worldwide[5]. Antipsychotic drugs have been considered as the primary treatment, which have significant benefits in psychotic symptoms but induce some healthy problems, such as obesity, metabolic syndrome, cardiovascular diseases, sexual disorders, sexual dysfunction and osteoporosis[6]. Previous studies demonstrated that patients with schizophrenia

had higher risk of experiencing low BMD and osteoporosis, as compared with the general population[2, 7].

The underlying mechanisms for decreased BMD and osteoporosis in schizophrenia patients are still unclear. Except for poor nutrition, reduced physical activity, excessive smoking and drinking, the main cause of osteoporosis in schizophrenia patients is the intake of antipsychotic medication[3, 8]. Antipsychotics can elevate the secretion of prolactin (PRL) through the dopamine D2 receptor-blocking effect[9]. And hyperprolactinemia caused by antipsychotics leads to the deficiency of estrogen and androgen, which can further accelerate bone loss and increase the risk of osteoporosis[10]. Ample evidences support that decreased estrogen levels can increase bone resorption by prolonging the life of osteoclasts[11, 12], and androgen deficiency can lead to the imbalance of osteoblast and osteoclast activity, resulting in decreased osteogenesis[13]. Taken together, abnormal levels of gonadal hormone may be associated with osteoporosis in schizophrenia patients. However, much of the existing research in this area recruited schizophrenia patients with different or mixed antipsychotics, which may preclude the conclusion to some extent.

In the clinical practice, risperidone is a widely used second generation antipsychotic (SGA), and also a prolactin-elevating SGA compound[14]. Early studies in schizophrenia patients treated with risperidone found high PRL levels to be associated with low BMD values[15]. However, other studies failed to replicate it[16]. The inconsistent result may be related to uncontrolled confounding factors, such as small sample size and physical activity.

In the present study, we aimed to explore the relationship between gonadal hormone and

BMD in long-term risperidone-treated schizophrenia inpatients, and to control the effects of physical exercise, diet and different antipsychotics on BMD to a certain degree. We expect our work to provide important information of the overall role of risperidone in regulating bone mineral density and gonadal hormone in schizophrenia patients.

2. Materials and Methods

2.1. *Participants*

A total of 250 inpatients with schizophrenia were included in our present study. All patients met the following criteria: (1) had been diagnosed with schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV); (2) age 18-75 years, Han Chinese; (3) patients were receiving SGAs risperidone treatment only at least 6 months. They were excluded if they: (1) had other diagnosed psychiatric disorder besides schizophrenia or a lifetime substance abuse/dependence disorder; (2) severe cardiovascular, hepatic, or renal diseases that affect bone metabolism, such as diabetes and hyperthyroidism; (3) were pregnant or breastfeeding; (4) history of bone fracture within one year prior to the enrollment. Since admission, all patients had the same diet structure, the regular schedule of activities in this hospital, and to minimize the difference in physical exercise, diet between patients. We also recruited 288 age- and sex-matched healthy control subjects, who were screened by a specialized psychiatrist using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders-Patient Edition. This study was performed in strict accordance with the Declaration of Helsinki and other relevant national and international regulations. All procedures for this study were reviewed and approved by the Institutional Review Boards of the Wenzhou Kangning hospital(20180412001), and written informed consent was obtained from each participant prior to the performance of any procedures related to this study.

2.2. *Measurement of anthropometric variables*

Detailed retrospective interviews were administered by psychiatrists to participants who met the study criteria to obtain the demographic and clinical information. Body weight and height were measured in a standardized manner, and body mass index (BMI) was calculated as weight in kg/square of height in meters. The subjects were barefooted and stand upright while height was measured to the nearest millimeter. An electronic scale was used to evaluate weight with light indoor clothes on.

2.3. *Bone Mineral Density Measurement*

BMD (g/cm^2) of the calcaneus was measured by a trained ultrasound technician blind to the status of the subjects in a separate examination center at the hospital using the 3.01 Sahara Clinical Bone Sonometer (Hologic). Quantitative ultrasound of calcaneus (QUS) measurements were performed at the right heel (or left heel if inaccessible), with 6 Broadband ultrasound attenuation (BUA; db/MHz) and speed of sound (SOS; m/s) at least twice on each calcaneum. The T-score of QUS refers to the number of standard deviations (SD) away from the mean T-score of a database of normal values compiled from a healthy young adult population, and it was calculated by (0.67 × BUA + 0.28 × SOS) – 420. We used the World Health Organization (WHO) criteria (World Health Organization Study Group, 1994) for the BMD results. Osteoporosis is defined as T-score to be −2.5 or more SD (i.e., T-score ≤ −2.5), osteopenia (low bone mass) as T-score ≥ 1 SD but < 2.5 SD below the mean value of healthy young adults (i.e., −1 >T > −2.5). Normal

BMD is defined as a T-score within one SD of healthy young adults (i.e., T-value > −1.0). Patients were classified into with and without osteoporosis groups according to the T-score.

2.4. *Serumgonadal hormone measurements*

A total of 10 ml fasting blood samples from the schizophrenia patients were drawn in ice-cooled ethylenediaminetetraacetic acid tubes between 6:00 and 9:00 a.m. Serum was separated by centrifugation at 5 °C and stored at − 20 °C. Serum fasting gonadal hormone including PRL, estradiol (E2), testosterone (T), progesterone (P), follicle-stimulating hormone (FSH), luteinizing hormone (LH) were measured using the chemiluminescence immunoassay kits ARCHITECT and ARCHITECT i2000 (Abbott Japan Co., Chiba, Japan).

2.5. *Statistical analysis*

Statistical analyses were performed using the SPSS software version 23.0 (SPSS, Chicago, IL). We used the independent Student's t-test or analysis of variance (ANOVA) for continuous variables and chi-squared for categorical variables to compare the differences between groups. In addition, Analysis of covariance (ANCOVA) was used for confounding variables controlled. Pearson correlation coefficients were calculated to examine the relationships between gonadal hormone levels and BMD in schizophrenia patients. Finally, the stepwise multiple logistic regression analyses (forward selection) were used to identify significant predictive variables associated with BMD or osteoporosis in schizophrenia patients, with entry and removal probabilities set at 0.01 and 0.05, respectively. All statistical tests were two tailed and statistical significance was set in alpha ≤ 0.05.

153 **3. Results**

154 3.1. *Demographic characteristics of patients and controls*

155 The demographic data of the subjects is presented in Table 1. The average age of patients
156 was 46.34±10.60 years, ranging from 23 to 77 years. The average BMI of patients was
157 24.46±3.96 kg/m^2. The mean age of the healthy controls was 46.00±10.77 years, ranging 21–76
158 years. The average BMI of controls was 23.44±3.50 kg/m^2. Our results showed that patients had
159 higher BMI levels compared to healthy control groups ($t = 3.165$, $P < 0.001$), which we adjusted
160 for in the following analysis. There were no significant differences in sex, smoking and drinking
161 status between patients and controls (All $P > 0.05$). In the present study, all schizophrenia
162 patients were hospitalized. The mean age of onset was 25.19±3.92 years, ranging from17 to 42
163 years. The average duration of illness was 21.15 ±9.38 years, ranging from 3 to 50 years.

164

165 *3.2. Prevalence of osteoporosis in patients and controls*

166 Our results showed that the frequency of osteoporosis was 24.4% (61/250) for the patients
167 with schizophrenia and 10.1% (29/288) for the healthy control group, Patients had a significant
168 higher incidence rate of osteoporosis than control groups ($X^2 = 19.730$, $P < 0.001$). We further
169 used logistic regression analysis to control for the socio-demographic confounders, such as age,
170 sex, BMI, smoking and drinking status, there was still a significant difference in the incidence
171 rate of osteoporosis between patients and control groups, with an adjusted OR of 3.197 ($X^2 =$
172 20.399, $P < 0.001$). In addition, BMD levels and BMD T-score were markedly lower in
173 schizophrenia patients compared to healthy control subjects ($t = 3.540$, $P < 0.001$; $t = 4.353$, $P <$

174 0.001, respectively).After controlling for the confounders, there were still significant differences
175 (F = 24.467, P < 0.001; F = 20.478, P < 0.001, respectively).
176
177 3.3 *Demographic clinical variables andgonadal hormone between patients with osteoporosis*
178 *and without osteoporosis*
179 Our results showed that schizophrenia patients with osteoporosis were older than
180 those without osteoporosis (t = 4.724, p < 0.001). Moreover, patients with osteoporosis had
181 longer duration of illness (t = 5.106, P < 0.001), higher proportion of smoking (t = 6.696, P =
182 0.013), lower BMI levels (t = 3.471, P < 0.001) compared to those without osteoporosis. There
183 were no significant differences in sex, age of onset, daily dosage of risperidone, drinking habit
184 and family history between patients with and without osteoporosis (All P > 0.05). Patients with
185 osteoporosis had lower BMD (t = 10.969, P < 0.001) and BMD T-score (t = 20.078, P < 0.001)
186 compared to those without osteoporosis (See in Table 2). These significant differences still
187 existed after age, sex, total disease courses, daily dosage of risperidone, smoking habit and BMI
188 were controlled (F = 198.050, P < 0.001; F= 198.467, P < 0.001, respectively). As for gonadal
189 hormone, our results showed that patients with osteoporosis had higher PRL (t = 17.626, P <
190 0.001), lower E2 (t = 7.183, P < 0.001) and P levels (t = 2.185, P = 0.030) compared to those
191 without osteoporosis (See in Table 2). The significant differences in serum PRL and E2 levels
192 between patients with and without osteoporosis also remained after adjusting for confounding
193 variables (F = 258.563, P < 0.001; F= 38.366, P < 0.001, respectively) (See in Figure 1).
194

195 *3.4 Risk factors for BMD or osteoporosis in schizophrenia patients*

196 Our correlation analysis showed significant correlations between BMD and age (r = -0.271,
197 P<0.001), total disease courses (r = -0.264, P < 0.001), the daily dosage of risperidone (r = -
198 0.206, P = 0.001), PRL (r = -0.364, P < 0.001) and E2 levels (r = 0.830, P < 0.001) in
199 schizophrenia patients. Further controlled the confounding variables such as age, sex, BMI, total
200 disease courses, the daily dosage of risperidone, smoking and drinking habits, the significant
201 associations between BMD and PRL (r = -0.697, P < 0.001) or E2 (r = 0.423, P < 0.001) levels
202 were still remained (See in Figure 2). In addition, the PRL levels in schizophrenia patients was
203 negative correlated with E2 levels (r = -0.224, P < 0.001).

204 Finally, a stepwise multiple logistic regression was utilized to identify the risk factors for
205 osteoporosis, showing that total disease courses (beta = 0.095, Wald x^2 = 8.544, P = 0.003),
206 smoking habit (beta = 1.429, Wald x^2 = 4.237, P = 0.040), PRL (beta = 0.113, Wald x^2 = 42.543,
207 P < 0.001) and E2 levels (beta = -0.026, Wald x^2 = 8.482, P = 0.004) were independently
208 responsible for the occurrence of osteoporosis in schizophrenia patients (See in Table 3).

209

210 **4. Discussion**

211 In the present study, we found that schizophrenia patients had higher rates of osteoporosis and
212 lower BMD compared to healthy controls, which is agreement with the majority of previous
213 studies[2, 17]. A recent meta-analysis reported that osteoporosis is over two and a half times more
214 common in schizophrenia patients treated with antipsychotics compared with age- and sex-
215 matched healthy controls[16]. Since different antipsychotics were used in schizophrenia patients

recruited in most previous studies, the rate of osteoporosis in schizophrenia patients may be affected. To our best knowledge, this is the first study exploring the prevalence of osteoporosis among schizophrenia inpatients with risperidone monotherapy. The present study demonstrated that approximately 24.4% of patients treated with risperidone have osteoporosis, and the risk for osteoporosis was 3.197 times independent of age, sex, BMI, smoking and drinking status compared to healthy controls. The higher rate of osteoporosis reported in present studies and combined with previous research results further supported that risperidone have notorious effects on the occurrence of osteoporosis[14, 15, 18].

Despite ample investigations, the precise role of antipsychotics in BMD loss and osteoporosis is not adequately known. One of the promising mechanisms was related with the derangement of hypothalamo–pituitary–gonadal axis induced by antipsychotics[19]. The dopamine D2 receptor-blocking effect of antipsychotics could elevate the secretion of PRL, causing hyperprolactinemia[20]. An increased PRL level then leads to the reduced secretion of and consequently lowers the secretion of sex hormones such as E2 and T[2, 10]. Interestingly, there exist available data suggesting that

Sex steroid hormones, estrogens and testosterones, play key roles in the develop and maintain the balance between bone resorption and formation[21, 22]. Since different type of antipsychotics exist different effects on PRL, recent meta-analysis or systematic review demonstrated that schizophrenia patients treated with PRL-raising antipsychotics (typical antipsychotics, risperidone, paliperidone, amisurlpride) had higher risk for BMD loss and osteoporosis compared to patients receiving PRL-sparing antipsychotics[23, 24]. Risperidone, as a widely used

SGA, which poorly penetrated the blood-brain barrier, therefore conducted longer-lasting D2 antagonism effects in the pituitary compared to the central nervous system. Ultimately, leading to a prolonged hyperprolactinemia and the maximal loss of BMD[25]. Taken together, Risperidone may be one of the most notorious antipsychotics to cause aberrant secretion of hypothalamo–pituitary–gonadal axis related hormone and to induce BMD loss. Hence, risperidone should be paid sufficient attention in the clinical practice.

To date, no study conducted to explore the relationship between hypothalamo–pituitary–gonadal axis related hormone and osteoporosis in schizophrenia with risperidone monotherapy, and to identify which gonadal hormone is responsible for the BMD loss and osteoporosis in those schizophrenia patients. Our present study provided a new recognition of this boundedness and further supported the role of gonadal hormone in osteoporosis in schizophrenia patients receiving risperidone. We found that patients with osteoporosis had significantly higher PRL but lower E2 levels compared to patients without osteoporosis, which is similar to the findings of previous studies[26]. Moreover, the correlation analysis and logistic regression analysis revealed that PRL, E2 and T were independent predictive factors associated with BMD or osteoporosis in schizophrenia patients. Despite some research demonstrated significant correlation between P, FSH, TH and reduced BMD[27, 28], our present study failed to discovered, which is in line with the majority of previous studies[29, 30]. The above results in accordance with the phenomenon of high incidence rate of osteoporosis in postmenopausal women and support the role of estrogen involved in bone metabolism.

In addition, our present study showed that schizophrenia patients with osteoporosis were

older and had longer total disease course compared to those without osteoporosis. These two risk factors have also been reported in early[2, 31, 32]. As we know, aging process increase of bone destruction but decrease of bone formation[23]. Schizophrenia patients with longer disease courses may receive a longer treatment with antipsychotics, thus, lead more profound effects on gonadal hormone. However, the relationship between BMD or osteoporosis and disease courses should be further verified in prospective and longitudinal study.

Furthermore, we found that lower weight and BMI in schizophrenia patients with osteoporosis compared to patients without osteoporosis. Ample evidence indicates that schizophrenia patients treated with SGA are at increased risk of developing metabolic abnormalities such as weight gain and obesity[33, 34]. Importantly, the high body weight or BMI effect of SGA could counteract their BMD loss effect in schizophrenia[35]. The significant positive correlation between body weight or BMI and BMD has been reported in numerous previous studies[1, 36]. As risperidone shows slighter effect on body weight and BMI compared to olanzapine or clozapine[37, 38], thus, exists more remarkable influence on osteoporosis[14]. Taken together, the above findings suggest that higher body weight is a protective factor for bone density to some extent in the schizophrenia patients. The potential protective mechanism may be related to the secretion of bone active hormones such as insulin and amylin from the pancreatic beta cells[39], but need to be confirmed with extensive longitudinal research.

Alcohol and cigarette use have also been reported to be risk factors for BMD loss[40-42], while some studies did not find any differences in drinking and smoking habits between patients with and without osteoporosis[2, 43]. In the present study, we only found higher smoking rate in

schizophrenia patients with osteoporosis compared to patients without osteoporosis. Our stepwise multiple logistic regression analysis further demonstrated that smoking was an independently risk factor for osteoporosis in schizophrenia patients with risperidone monotherapy. It is well known that schizophrenia patients had high prevalence of smoking and even nicotine dependence compared to normal controls[44]. An early meta-analysis demonstrated that current smoking increased the risk of any body fracture by 25% compared to non-smokers[45]. However, the reasonable explanations for the mechanical relationship between smoking and reduced BMD are obscured and warrant investigation in further.

The strength of this study is that we explored the relationship between gonadal hormone and BMD loss and osteoporosis in schizophrenia patients with risperidone monotherapy by a comparatively large sample size. In addition, we only recruited inpatients with the same diet structure and similar physical intensity, thus, to minimize the disturbance of those factors on our conclusions. However, several limitations of this current study should also be mentioned here. First, the cross-sectional nature of the research had a limited capacity to identify a causal relationship between gonadal hormone and BMD loss or osteoporosis. Second, since the patients were all inpatients recruited from one hospital in Wenzhou in this survey, our findings could not be generalized to other settings and outpatients. Third, although all schizophrenia patients with risperidone monotherapy for at least 6 months before recruited, we did not collect detailed information about medication used before, which may have some effects on gonadal hormone and BMD in schizophrenia patients. Ultimately, future research with prospective and longitudinal design is required to evaluate causal relations between gonadal hormone and BMD

in the first-episode and drug-naïve schizophrenia patients.

In summary, our results indicated an increased prevalence of osteoporosis and BMD loss in schizophrenia patients with risperidone monotherapy compared to normal controls. Patients with osteoporosis were older, displayed longer disease courses, higher weight, BMI and smoking rate, had significant higher PRL levels but lower levels of E2 and T compared to those patients without osteoporosis. In addition, our stepwise multiple logistic regression showed that total disease courses, smoking habit, PRL and E2 levels were independently responsible for the occurrence of osteoporosis in schizophrenia patients. our findings provided suggestive evidence that gonadal hormone, especially PRL and E2, together with environment risk factors including smoking were related to BMD loss and osteoporosis in schizophrenia patients treated with risperidone, however, our preliminary conclusion should be verified by prospective and longitudinal study and further to investigate its mechanism.

Abbreviations

BMD：Bone Mineral Density；BMI：Body Mass Index；PRL：Prolactin；E2：estradiol ；T：Testosterone；P：Progesterone；FSH：follicle-stimulating hormone；LH：luteinizing hormone；SGA：Second Generation Antipsychotic

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Conflicts of Interest

The authors have no conflicts to disclose.

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Figure Legends

Figure 1. Comparisons of serumprolactin and Estradiollevels between schizophrenia patients with osteoporosis and without osteoporosis.
P value was calculated by adjusting for the characteristics including age, sex, total disease courses, daily dosage of risperidone, BMI, smoking and drinking habit.
Each bar represents the mean level of prolactin or Estradiol. Error bars represent the standard deviation (SD).
Abbreviations: BMD, bone mass density.

Figure 2. Correlations between bone mass index and serum prolactin or Estradiol levels in schizophrenia patients.
Abbreviations: BMD, bone mass density.

Table 1(on next page)

Comparison between schizophrenia patients and control subjects

BMI: body mass index, BMD: bone mass density

Table 1 Comparison between schizophrenia patients and control subjects.

	Patients (N=250)	Controls (N=288)	t/X^2	P
Age (year)	46.34±10.60	46.00±10.77	0.364	0.716
Sex (male/female)			2.800	0.094
Male	137	137		
Female	151	113		
BMI (kg/m^2)	24.46±3.96	23.44±3.50	3.165	< 0.001
Drinking			2.25	0.133
Yes	41	66		
No	209	242		
Smoking			0.908	0.341
Yes	57	56		
No	193	232		
BMD (g/cm^2)	0.45±0.09	0.47±0.08	3.540	< 0.001
T-score	-1.50±1.41	-1.01±1.13	4.353	< 0.001
Osteoporosis			19.730	< 0.001
Yes	61	29		
No	189	259		

BMI: body mass index, BMD: bone mass density,

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Table 2(on next page)

Differences between schizophrenia patients with osteoporosis and without osteoporosis

BMI: body mass index, BMD: bone mass density, E2: Estradiol , T: Testosterone, P: Progesterone , PRL: prolactin , FSH: Follicle-stimulating hormone, LH: luteinizing hormone.

1 Table 2 Differences between schizophrenia patients with osteoporosis and without osteoporosis.

	Patients with osteoporosis	Patients without osteoporosis	t/X^2	P
	N =61	N =189		
Age (year)	51.69±11.59	44.61±9.67	4.724	< 0.001
Sex (male/female)	40/21	97/92	3.781	0.052
Drinking (yes/no)	12/49	29/160	0.630	0.427
Smoking (yes/no)	21/40	36/153	6.196	0.013
Age of onset (year)	25.46±3.79	25.11±3.97	0.611	0.542
Course of disease (year)	26.23±9.34	19.51±8.81	5.106	< 0.001
Family history (yes/no)	5/56	15/174	0.004	0.948
Height (cm)	162.30±7.53	162.96±7.69	0.590	0.555
Weight (kg)	61.10±9.72	66.07±12.08	3.267	0.001
BMI (kg/m^2)	23.14±3.06	24.86±4.13	3.471	0.001
Daily dosage of risperidone	4.75±1.71	4.72±1.92	0.125	0.900
BMD (g/cm^2)	0.35±0.07	0.48±0.08	10.969	< 0.001
T-score	-3.26±0.68	-0.93±1.07	20.078	< 0.001
E2 (pmol/L)	55.28±24.61	88.03±45.32	7.183	< 0.001
T (nmol/L)	9.21±5.51	8.86±6.25	0.388	0.698
P (nmol/L)	0.63±0.29	0.73±0.46	2.185	0.030
PRL (ug/L)	90.88±20.47	44.05±17.20	17.626	<0.001
FSH (IU/L)	7.59±4.10	6.61±3.97	1.661	0.098
LH (IU/L)	8.99±3.51	8.77±4.42	0.397	0.692

2 BMI: body mass index, BMD: bone mass density, E2: Estradiol, T: Testosterone, P: Progesterone, PRL:
3 prolactin, FSH: Follicle-stimulating hormone, LH: luteinizing hormone.
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Table 3(on next page)

Results of the stepwise logistic regression analysis: independent risk factors for osteoporosis in schizophrenia patients

E2: Estradiol , PRL: prolactin

Table 3. Results of the stepwise logistic regression analysis: independent risk factors for osteoporosis in schizophrenia patients.

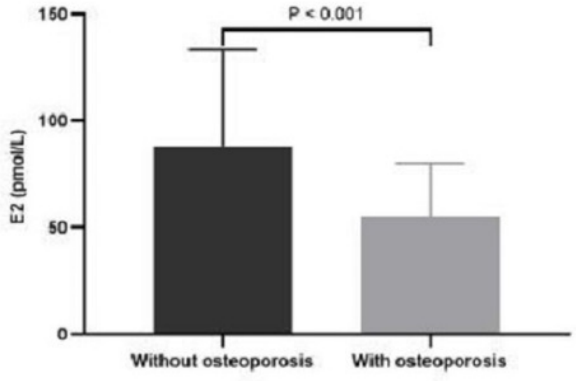
Predictors	B	SE	Wald	Standard B	Exp.(B)	Sig	95%CI for Exp.(B)
Total disease courses	0.095	0.033	8.544	0.475	1.100	0.003	1.032~1.173
Drinking habit	1.429	0.694	4.237	0.350	4.175	0.040	1.071~16.281
E2	-0.026	0.009	8.482	-0.353	0.974	0.004	0.957~0.991
PRL	0.113	0.017	42.543	2.036	1.119	<0.001	1.082~1.158

E2: Estradiol, PRL: prolactin

Figure 1

Comparisons of serum prolactin and Estradiollevels between schizophrenia patients with osteoporosis and without osteoporosis.

P value was calculated by adjusting for the characteristics including age, sex, total disease courses, daily dosage of risperidone, BMI, smoking and drinking habit. Each bar represents the mean level of prolactin or Estradiol. Error bars represent the standard deviation (SD).



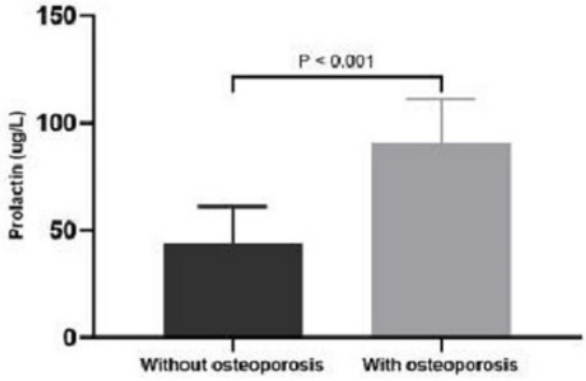


Figure 2

Correlations between bone mass index and serum prolactin or Estradiol levels in schizophrenia patients

Abbreviations: BMD, bone mass density.