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ORIGINAL RESEARCH

Analysis of the Influencing Factors of Aripiprazole and Risperidone on Bone Mass Health in Patients with Chronic Schizophrenia: A Cross-Sectional Study

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Purpose: Patients with schizophrenia have obvious bone health problems. However, the differences in the effects of risperidone and aripiprazole on the bone health of schizophrenia patients remain unclear. This study aims to analyze the effects of risperidone and aripiprazole on the bone health of patients with schizophrenia.

Patients and Methods: A total of 210 chronic schizophrenia patients aged 35–55, who had been on regular maintenance therapy with either risperidone or aripiprazole for more than 5 years, were recruited. Demographic data, clinical characteristics, and laboratory indicators were collected. Bone mineral density (BMD) was measured using the UBS-3000plus Quantitative Ultrasound Bone Densitometer Measurement System. Pearson correlation analysis and multiple logistic regression analyses were performed to explore the relationships between variables.

Results: The proportion of patients with bone mass decline in the risperidone group (55.32%) was significantly higher than that in the aripiprazole group (37.07%). BMD levels were negatively correlated with prolactin, progesterone, albumin, UA, negative score, and total disease duration, and positively correlated with estradiol, phosphorus, and creatinine. Multivariate logistic regression analysis showed that the use of aripiprazole was a protective factor against bone mass decline, while the negative score and prolactin were risk factors.

Conclusion: The bone health level of schizophrenia patients is significantly reduced. Long-term use of risperidone is associated with a more significant decrease in bone density compared with aripiprazole.

Keywords: schizophrenia, prolactin, aripiprazole, risperidone, bone mineral density

Introduction

Schizophrenia is a severe mental disorder that often correlates with significant impairments in patients' cognitive, emotional, and behavioral functions, thereby affecting their occupational and social functions.[1] It is one of the main types of mental disabilities. The global incidence of schizophrenia is 1%, with variations in different regions.[2] In China, influenced by diagnostic criteria and cultural factors, the incidence rate ranges from 0.39% to 0.83%.[3] Patients with schizophrenia are susceptible to various complications by several factors, such as the impact of mental symptoms, side effects of medications, and nutritional deficiencies.[4–7] The occurrence of physical diseases in schizophrenia patients is much higher than that in the general population.[8]

Current research has shown that schizophrenia patients have obvious bone health problems.[9] Their risks of decreased bone density, reduced bone mass, or osteoporosis are significantly higher than those of the general population. Previous

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studies have indicated that approximately 50%-60% of patients have reduced bone density, and the risk of developing osteoporosis was 2–3 times that of the general population.[10] The risk of femoral neck fractures in long-term hospitalized patients increase by 2.8 times.[11] In addition, osteoporosis tends to be younger in schizophrenia patients. The proportion of patients under the age of 40 with schizophrenia who have reduced bone mass is significantly higher than that of the normal population.[12,13] The prevalence of osteoporosis in the general Chinese population is approximately 8.8% among individuals aged 40–59 years and 32.0% among those aged 60 years and above. This indicates that schizophrenia patients represent a high-risk group for bone health problems. Therefore, some studies have focused on the issue of bone health in patients with schizophrenia.

Negative symptoms of schizophrenia are closely related to osteoporosis, because negative symptoms can lead to insufficient physical activity, reduced outdoor time, and poor dietary status,[14] which in turn affect bone metabolism and reduce bone density. Positive symptoms may indirectly affect bone health by causing abnormal lifestyle and poor medication compliance, and the relationship between psychotic symptoms and bone density needs to be further verified in clinical studies.

According to recent research, the main factors influencing the changes in bone density in patients with schizophrenia include the following aspects: the use of second-generation antipsychotic drugs, hyperprolactinemia, significant negative symptoms, abnormal lifestyle, vitamin D or calcium deficiency, chronic inflammation, and decreased sex hormone levels.[13,15,16] Most of the second-generation antipsychotic drugs can cause a series of metabolic problems and an increase in prolactin levels.[17] The occurrence of metabolic syndrome can indirectly affect bone metabolism. Hyperprolactinemia accelerates bone loss by inhibiting the secretion of sex hormones.[18] Aripiprazole, as a new type of antipsychotic drug, can effectively reduce the occurrence of the aforementioned adverse reactions. Moreover, studies have shown that compared with other antipsychotic drugs, the impact of aripiprazole on osteoporosis in patients with schizophrenia may be relatively mild.[19] However, there is currently a lack of a comparative study between risperidone and aripiprazole in terms of bone health issues.

Risperidone is a classic second-generation antipsychotic drug that is widely used in the clinical treatment of chronic schizophrenia, but previous studies have shown that risperidone has a significant effect on increasing prolactin levels,[17] and hyperprolactinemia is a key risk factor for bone mass decline in patients with schizophrenia.[18] Aripiprazole is a new type of partial D2 receptor agonist with little effect on prolactin levels,[20] and its impact on bone health is unclear. Therefore, selecting risperidone and aripiprazole for head-to-head comparison can directly explore the association between antipsychotic-induced prolactin changes and bone mass health in patients with chronic schizophrenia, and provide clinical evidence for the rational selection of antipsychotic drugs.

Therefore, in order to further clarify the effects of risperidone and aripiprazole on the bone health of patients with schizophrenia, this study compared the bone density of patients with chronic schizophrenia who had been taking risperidone or aripiprazole for a long time, and identified the advantages of different antipsychotic drugs in treatment.

Materials and Methods

Settings and Subjects

This study is a single-center exploratory cross-sectional study. Study hypothesis: (1) Long-term use of risperidone is associated with a higher proportion of bone mass decline in patients with chronic schizophrenia compared with aripiprazole; (2) Prolactin levels and negative symptom scores are positively associated with the risk of bone mass decline; (3) Aripiprazole use is a protective factor for bone mass decline in patients with chronic schizophrenia after adjusting for confounders.

The study was conducted from January 2023 to December 2023 in the inpatient and long-term rehabilitation wards of a psychiatric hospital in Beijing, China. All subjects were inpatients or long-term rehabilitation patients with chronic schizophrenia, and the living environment and lifestyle were relatively unified. In this study, schizophrenia patients aged 35–60 years old. We refer to previous studies, they were reassessed using the Mini International Neuropsychiatric Interview (M.I.N.I.) according to the diagnostic criteria of the International Classification of Diseases (ICD-10). All subjects had a disease duration of more than 5 years and were currently on regular maintenance therapy with an

antipsychotic drug (risperidone or aripiprazole). Subjects with one or more of the following conditions were excluded: (1) Patients taking any medications known to be risk factors for BMD decline, such as antidepressants, anticonvulsant drugs, glucocorticoids, or immunosuppressive drugs; (2) Patients with diseases known to be risk factors for BMD decline, such as alcohol dependence, chronic kidney disease, hepatorenal dysfunction, serious digestive system diseases, blood diseases, malignant tumors, diabetes, thyroid and thyroid function changes; (3) Patients who could not engage in normal activities or had activity restrictions due to major diseases.[21]

Clinical Assessments

The ICD-10 was used as the diagnostic criteria for schizophrenia patients. The survey was conducted by two trained and qualified investigators. We used the case report form to collect general information about the subjects, including demographic data and disease-related information such as name, age, sex, date of birth, education, occupation, age of onset, duration of illness, previous illnesses and medication history, smoking and alcohol use history, daily exercise, and current medication list. The severity of mental symptoms was evaluated using the Positive and Negative Syndrome Scale (PANSS),[14] and the positive scale score, negative scale score, and total score were recorded.

All subjects received monotherapy of risperidone or aripiprazole for more than 5 years, with no prior exposure to other second-generation antipsychotic drugs and no switching of antipsychotic drugs during the study period. The drug dose was adjusted to the maintenance dose according to the patient's clinical symptoms, and the dose was stable for more than 6 months before recruitment.

Laboratory Assessments

Blood draws were completed between 7 am and 9 am the next morning by specially trained research nurses after the patients had fasted for 8–12 hours. The blood sample (5 mL) was allowed to stand at room temperature for 1 hour and then centrifuged at 3000 rpm for 5 minutes. Approximately 1.5 mL of serum was separated and carefully transferred to a disposable cup, and stored in an ultra-low (−80°C) refrigerator until analysis. Before the detection, the stored serum samples were taken out from the −80°C refrigerator and placed in a 4°C refrigerator to thaw. They were allowed to stand at room temperature for equilibration and were detected within 48 hours on the day of detection. The test items included liver function, kidney function, blood lipid, blood sugar, sex hormones, thyroid function, etc.

The detections of hormones, fasting blood glucose (FBG), total cholesterol, calcium, and phosphorus were batch-completed by standardized trained technical staff at the Clinical Laboratory of the hospital.

Bone Mineral Density Assessment

Bone density was measured using the UBS-3000plus Quantitative Ultrasound Bone Densitometer Measurement System (Shaanxi Chaoshi Electronic Technology Co., Ltd., China), which has been validated by the China Food and Drug Administration (CFDA approval number: 20172070658) and has good consistency with dual-energy X-ray absorptiometry (DXA) for forearm bone density measurement (correlation coefficient $r = 0.89$, $p < 0.001$). The 1/3 distal forearm ulna (fixed anatomical site) was selected as the unified measurement site for all subjects, and the measurement was completed by the same trained operator to ensure the consistency of the operation. The primary quantitative ultrasound (QUS) parameters measured included speed of sound (SOS, m/s) and broadband ultrasound attenuation (BUA, dB/MHz), and the T-score was calculated by comparing the measured values with the China ethnic group database built into the instrument (for 30–50 years old ethnic and gender-specific peak bone mass). According to the World Health Organization (WHO) diagnostic criteria adapted for QUS forearm measurement, the bone mass status was classified as: normal bone mass (T-score > -1.0), bone mass decline (osteopenia, $-2.5 <$ T-score ≤ -1.0), and osteoporosis (T-score ≤ -2.5). All subjects were measured 3 times, and the average value was taken as the final measurement result to reduce the measurement error.

Statistical Analysis

SPSS 24.0 statistical software was used for data analysis. Categorical variables were analyzed using the chi-square test, and continuous variables were analyzed using the independent samples *t*-test. Pearson correlation analysis was used to explore the correlation between variables and bone mass decline. Multiple logistic regression analysis was used to build two models:

Model 1 (unadjusted) included aripiprazole use, negative score and prolactin levels; Model 2 (adjusted) added key confounders including age, sex, BMI, smoking status, alcohol use status, physical activity level and (for female patients) menopausal status to adjust for their potential effects on bone density. The level of significance was set at 0.05 (two-tailed). Stratification analysis was performed by sex (male/female) and for female patients by menopausal status (premenopausal/postmenopausal) to explore the association between antipsychotic drugs and bone mass decline in different subgroups.

The predictors included in the multiple logistic regression model were determined based on previous literature reports and clinical relevance, including aripiprazole use, negative score, prolactin levels and key confounders. Missing data handling: The proportion of missing data in this study was less than 5%, and the complete case analysis method was used for processing. Collinearity test: Variance inflation factor (VIF) was used to test the collinearity between predictors, and the VIF value of all predictors was less than 2, indicating no collinearity. Model performance evaluation: The Hosmer-Lemeshow goodness-of-fit test was used to evaluate the model fitting degree (Model 2: χ^2=7.25, p=0.51), and the area under the receiver operating characteristic curve (AUC) was 0.78 (95% CI: 0.71–0.85), indicating good model discrimination ability.

Results

Demographic Data

A total of 210 chronic schizophrenia patients were recruited in this study. Among them, 116 patients were taking aripiprazole (aripiprazole group), 35–59 years old (49.70±9.47), and the male-to-female ratio was 1:1. The proportion of patients meeting the bone mass decline criteria was 37.1%, and the proportion of patients meeting the osteoporosis diagnosis criteria was 3.4%. Ninety-four patients were taking risperidone (risperidone group), 36–60 years old (50.62 ±12.76), and the male-to-female ratio was also 1:1. The proportion of patients meeting the bone mass decline criteria was 55.3%, and the proportion of patients meeting the osteoporosis diagnosis criteria was 3.2%. The proportion of patients with bone mass decline in the risperidone group was significantly higher than that in the aripiprazole group. There was no significant difference in the proportion of osteoporosis between the two groups.

The PANSS negative score and total disease duration of schizophrenia patients in the bone mass decline group were higher than those in the normal bone mass group, with statistical significance. There were no significant differences in the male-to-female ratio distribution, PANSS total score, PANSS positive score, and equivalent drug dose between the two groups (See Table 1).

Table 1 Demographic and Clinical Characteristics

	Aripiprazole Group (n = 116)	**Risperidone Group (n = 94)**	**T-value/χ^2 value**	**p - value**
Bone density	−0.71±1.10	−1.16±0.92	3.15	0.16
Proportion of bone mass decline	37.07% (43/116)	55.32% (52/94)	6.98	0.01
Proportion of osteoporosis	3.45% (4/116)	3.19% (3/94)	0.00	1.00
	Bone Mass Decline Group (n = 95)	**Normal Bone Mass Group (n = 115)**	**T-value/χ^2 value**	**p - value**
Age	51.58±10.08	49.07±9.69	2.94	0.14
Disease duration	21.43±8.89	18.19±10.05	2.45	0.02*
Height	167.96±5.93	168.75±6.73	1.71	0.08
Weight	76.77±13.29	75.64±11.34	2.96	0.09
Body mass index	26.70±3.93	25.57±4.23	1.98	0.05
Equivalent dose (CPZ)	260.27±195.76	258.34±185.72	0.07	0.94
Proportion of aripiprazole use	43/52	73/42	6.98	0.01*
PANSS total score	82.65±11.32	81.68±10.88	0.63	0.53
PANSS positive score	17.29±5.19	16.86±5.27	0.60	0.55
PANSS negative score	29.95±5.72	28.33±3.74	2.37	0.02*

Notes: *p < 0.05, compared with the control group; χ^2 = chi-square value, T = t-value.

Differences in Hematological Indicators Between the Two Groups

Among the two groups of patients, the prolactin level in the bone mass decline group was significantly increased, while the levels of estradiol and progesterone were significantly decreased, and the blood phosphorus level was lower than that in the normal group, with statistical significance between the two groups. The prolactin level in the risperidone group (55.61±39.76) was significantly higher than that in the aripiprazole group (41.93±35.29) (t=−2.64, p=0.01, Cohen's d=0.38, 95% CI for mean difference: 3.25–25.11) (See Table 2).

Correlation Between Bone Mass Decline and Differential Indicators and Multivariate Regression Analysis

According to the results of Pearson correlation analysis, changes in bone density were negatively correlated with factors such as prolactin (r= - 0.85, p<0.01), progesterone (r= −0.25, p<0.01), albumin (Alb) (r= −0.17, p= 0.01), UA (r= −0.17, p= 0.02), negative score (r= −0.20, p= 0.01), and total disease duration (r= −0.25, p < 0.01). They were positively

Table 2 Hematology Test Results

	Aripiprazole Group (n = 116)	**Risperidone Group (n = 94)**	**T-value**	**p-value**
Prolactin	41.93±35.29	55.61±39.76	−2.64	0.01*
Estradiol	34.18±28.62	28.13±11.45	2.08	0.04*
Progesterone	0.29±0.26	0.28±0.16	0.24	0.81
Testosterone	15.77±12.23	14.00±7.79	1.28	0.22
	Bone Mass Decline Group (n = 95)	**Normal Bone Mass Group (n = 115)**	**T-value**	**p - value**
Testosterone	14.19±10.35	15.63±10.60	−0.99	0.32
Estradiol	28.45±12.82	33.96±28.29	−1.75	0.08*
Prolactin	80.60±33.90	21.17±8.46	18.14	0.00**
Progesterone	0.32±0.31	0.25±0.10	2.10	0.04*
TSH	3.07±1.93	3.17±3.71	−0.24	0.81
T3	0.97±0.18	0.94±0.15	1.34	0.18
FT3	2.64±0.30	2.65±0.32	−0.22	0.83
T4	24.92±118.99	16.32±70.52	0.65	0.52
FT4	0.86±0.14	0.82±0.11	2.41	0.02*
Ca	2.25±0.09	2.23±0.10	1.67	0.09
P	0.96±0.13	0.99±0.14	−1.56	0.12
GLU	4.52±0.61	4.53±0.80	−0.09	0.93
CHO	3.94±0.68	3.95±0.83	−0.02	0.99
TG	1.24±0.67	1.36±0.75	−1.21	0.23
LDL	2.46±0.70	2.53±0.84	−0.59	0.55
HDL	1.27±0.32	1.27±0.37	0.05	0.96
ALT	29.59±4.95	29.23±5.83	0.48	0.63
AST	27.79±6.73	29.03±6.47	−1.35	0.18
TP	75.76±4.91	74.48±4.93	1.87	0.06
Alb	48.04±4.30	46.68±4.16	2.32	0.02*
ALP	65.40±18.42	72.65±18.07	−2.87	0.01*
Urea	5.57±1.82	5.43±1.57	0.59	0.553
Cre	66.05±13.3	69.78±13.07	−2.04	0.04
UA	280.89±75.45	256.45±72.18	2.39	0.01*
Hcy	10.51±2.53	10.62±2.38	−1.25	0.10

Notes: *p < 0.05, **p < 0.01, compared with the control group; T = t-value.

Table 3 Correlation Analysis and Multiple Logic Regression Analysis of Bone Mineral Density Decline

Variables	Model 1 (Unadjusted)			Model 2 (Adjusted)		
	OR (95% CI)	p-value	B	OR (95% CI)	p-value	B
Use of aripiprazole	0.80 (0.69–0.95)	0.02*	−0.22	0.76 (0.65–0.89)	0.001**	−0.27
Negative scale score	1.25 (1.03–1.47)	0.02*	0.22	1.21 (1.01–1.45)	0.04*	0.19
Prolactin levels	1.37 (1.12–1.58)	0.00**	0.32	1.32 (1.10–1.59)	0.002**	0.28

Notes: *p < 0.05, **p < 0.01, compared with the control group.

correlated with factors such as estradiol (r= 0.21, p <0.01), phosphorus (P) (r= 0.16, p= 0.02), and creatinine (Cre) (r= 0.17, p= 0.01).

The results of multivariate logistic regression analysis indicated that the proportion of aripiprazole use was a protective factor against bone mass decline (odds ratio [OR]=0.80), suggesting that the use of aripiprazole might reduce the occurrence of bone mass reduction. On the other hand, the negative score (OR=1.25) and prolactin (OR=1.37) were risk factors for bone mass reduction. Therefore, it is necessary to pay close attention to the occurrence of related problems during the treatment of schizophrenia (See Table 3).

Sensitivity analysis with continuous BMD T-score as the outcome variable (linear regression) showed that after adjusting for age, sex, BMI and other confounders, risperidone use was still associated with a lower T-score (β=−0.32, p=0.001), and aripiprazole use was associated with a higher T-score (β=0.28, p=0.002), consistent with the results of the categorical outcome variable analysis.

Subgroup Analysis by Sex and Menopausal Status

In the male subgroup (n=105), the proportion of bone mass decline in the risperidone group (52.8%, 28/53) was significantly higher than that in the aripiprazole group (34.0%, 18/52) (χ^2=4.21, p=0.04). In the female subgroup (n=105), the proportion of bone mass decline in the risperidone group (57.8%, 24/41) was significantly higher than that in the aripiprazole group (39.6%, 25/64) (χ^2=3.98, p=0.047).

For female patients, the premenopausal subgroup (n=42) had a lower proportion of bone mass decline (35.7%, 15/42) compared with the postmenopausal subgroup (n=63) (57.1%, 36/63) (χ^2=6.02, p=0.014). In the postmenopausal female subgroup, the proportion of bone mass decline in the risperidone group (66.7%, 16/24) was significantly higher than that in the aripiprazole group (48.1%, 13/27) (χ^2=3.85, p=0.05).

Multivariate logistic regression analysis of the female subgroup adjusted for menopausal status showed that aripiprazole use was still a protective factor for bone mass decline (OR=0.72, 95% CI: 0.58–0.89, p=0.002), and prolactin levels (OR=1.30, 95% CI: 1.08–1.56, p=0.006) and postmenopausal status (OR=1.85, 95% CI: 1.12–3.06, p=0.016) were independent risk factors for bone mass decline.

Discussion

This study reveals that patients with chronic schizophrenia have bone health problems, which is consistent with previous research findings. The proportion of bone mass decline in the risperidone group (55.32%) and aripiprazole group (37.07%) in this study is similar to the results of a population-based study in Australia,[13] which found that the risk of low bone density in schizophrenia patients taking risperidone is 1.8 times that of patients taking aripiprazole, indicating the consistency and generalizability of the study results. The long-term use of certain antipsychotic drugs can significantly affect bone density.[21] Previous studies have shown that long-term blocking of the dopaminergic neural pathway can lead to the degeneration of the related pathway functions. The degenerated dopaminergic neural pathway affects bone formation by influencing the differentiation of bone cells. In animal studies, knocking out the DA receptors in mice can result in a significant reduction in bone density and affect the quality of bone development.[22,23] This may be one of the hypotheses that antipsychotic drugs cause bone mineral density reduction. In addition, glutamate is the main excitatory neurotransmitter in the central nervous system. Its hypofunction may lead to negative symptoms. Meanwhile, glutamate receptors are expressed in osteoblasts, and abnormal signals of these receptors may disrupt the balance of bone

remodeling, resulting in enhanced bone resorption.[22] Although antipsychotic drugs have a therapeutic effect on mental symptoms, they also pose certain threats to bone health. Therefore, antipsychotic drugs may have a negative impact on the bone health of patients.

In this study, the impact of neuroendocrine changes on bone density was the most significant, which was consistent with previous research results. Risperidone lacks partial agonist effects on the dopamine system. By blocking the D2 receptors on the anterior pituitary, it relieves the inhibitory effect of the hypothalamus on the adenohypophysis, resulting in increased prolactin secretion. Long-term elevated prolactin can cause abnormal feedback regulation of the hypothalamic-pituitary-gonadal axis, affecting the levels of multiple sex hormones. The neuroendocrine axis disorder caused by second-generation antipsychotic drugs may play a central role in bone health issues. The second-generation antipsychotic drugs (SGAs) can increase prolactin (PRL) levels by blocking dopamine D2 receptors.[24,25] High levels of prolactin can cause abnormal levels of estradiol (E2) and testosterone (T) by inhibiting the release of gonadotropin-releasing hormone from the hypothalamus. These sex hormones have a bidirectional regulatory effect on bone metabolism.[26–28] A prolonged state of low sex hormone levels can lead to an imbalance in bone turnover rate.[29,30] Therefore, according to this study, the use of aripiprazole can reduce the impact of endocrine disorders on the bones, thereby lowering the risk of related problems.

There is a complex relationship between the negative symptoms of schizophrenia (such as decreased willpower, emotional apathy, anhedonia, etc.) and osteoporosis.[31,32] In this study, negative symptoms were a significant risk factor for decreased bone mineral density. Negative symptoms, manifested as decreased willpower, anhedonia, social withdrawal, etc, directly lead to changes in patients' lifestyles, further exacerbating bone metabolism disorders.[33] Due to a lack of motivation, patients have long-term insufficient physical activity, which reduces the mechanical load on bones, inhibits osteoblast activity, and correlates with a decrease in bone density. Research shows that weight - bearing exercise can stimulate bone formation, while patients with negative symptoms have a 30%-58% faster bone mineral density reduction rate than the general population due to bed-rest or sedentary behavior.[34,35] Social withdrawal and reduced activity lead to less outdoor time, resulting in insufficient vitamin D synthesis in the skin. Vitamin D is a key regulator of calcium absorption, and its deficiency directly affects the bone mineralization process and increases the risk of osteoporosis.[36,37] Anhedonia and emotional apathy cause patients to neglect their dietary health, resulting in insufficient intake of nutrients such as calcium and protein. Studies have found that the daily calcium intake of schizophrenia patients is only 60%-70% of the recommended amount.[38]

Aripiprazole has partial agonistic effects on dopamine D2 receptors, which is associated with the improvement of negative symptoms in patients with schizophrenia. This study found that negative score is an independent risk factor for bone mass decline. It is possible that the improvement of negative symptoms by aripiprazole may indirectly reduce the risk of bone mass decline, but this hypothesis has not been verified by mediation analysis in this study and needs to be confirmed by subsequent longitudinal studies. The effect of antipsychotic drugs on bone metabolism has been reported in previous studies, and the result that risperidone is associated with a more significant bone mass decline is consistent with the existing research conclusions, which is relatively predictable.[13,18] The novelty of this study lies in the head-to-head comparison of aripiprazole and risperidone in a Chinese population of chronic schizophrenia patients with long-term monotherapy, and the confirmation of aripiprazole as an independent protective factor for bone mass decline after adjusting for multiple confounders. At the same time, this study supplemented the subgroup analysis results by sex and menopausal status, which provides more detailed clinical evidence for the bone health management of different subgroups of schizophrenia patients. Subgroup analysis showed that the association between risperidone use and higher bone mass decline proportion exists in both male and female subgroups, indicating that gender is not the main cause of the difference in bone density between the two groups. However, postmenopausal status is an additional risk factor for bone mass decline in female patients, which suggests that clinicians should pay more attention to the bone health of postmenopausal female patients taking risperidone.

The average T-score of the risperidone group (−1.16±0.92) was 0.45 lower than that of the aripiprazole group (−0.71 ±1.10). According to clinical practice, a T-score decrease of 0.5 is associated with a 10%-15% increase in the risk of osteoporotic fractures, which suggests that the difference in bone density between the two groups has certain clinical significance. However, this study did not measure fracture outcomes and cannot confirm the association between

antipsychotic drug use and fracture risk in patients with chronic schizophrenia, and future studies need to include fracture as an outcome variable for long-term follow-up. The clinical choice of antipsychotic drugs for patients with chronic schizophrenia should not only consider the improvement of mental symptoms, but also pay attention to the long-term safety and impact on the quality of life of patients.[39] Aripiprazole, as a partial D2 receptor agonist, not only has a good therapeutic effect on schizophrenia symptoms, but also has a relatively small impact on bone health and prolactin levels,[20] which is consistent with the results of this study that aripiprazole is a protective factor for bone mass decline.

This study is a cross-sectional design, which can only reveal the association between aripiprazole/risperidone use and bone mass health in patients with chronic schizophrenia, and cannot confirm the causal relationship between antipsychotic drugs and bone density changes. The lack of baseline bone density measurements and longitudinal follow-up data limits the ability to infer the dynamic changes of bone density and the causal effect of drugs on bone health. This study did not measure some key confounders affecting bone density, such as vitamin D status, dietary calcium/protein intake, and cumulative antipsychotic drug exposure dose. These unmeasured factors may have potential effects on the study results, and future studies need to include these indicators for comprehensive analysis. This study is an exploratory analysis to explore the influencing factors of bone mass health in patients with chronic schizophrenia taking antipsychotic drugs, and no multiple comparison correction was performed for the statistical results, and the conclusions need to be verified by subsequent confirmatory studies. All subjects in this study have a disease duration of more than 5 years and have received long-term antipsychotic treatment for more than 5 years. Long-term disease duration and long-term medication use may have a cumulative effect on bone health, and this study cannot separate the independent effects of disease duration and drug use on bone density. Future studies need to include patients with different disease durations and medication durations to explore the cumulative effect of antipsychotic drugs on bone health. No formal sample size calculation was performed, which is a limitation of this study, and the results need to be verified by large-sample multicenter studies.

Conclusion

This cross-sectional study found that the bone health level of patients with chronic schizophrenia is significantly reduced, and long-term monotherapy of risperidone is associated with a more significant decrease in bone density compared with aripiprazole. After adjusting for age, sex, BMI, menopausal status and other key confounders, aripiprazole use is an independent protective factor for bone mass decline in patients with chronic schizophrenia, while negative symptom score and prolactin level are independent risk factors. Subgroup analysis showed that this association exists in both male and female subgroups, and postmenopausal status is an additional risk factor for bone mass decline in female patients.

The clinical implication of this study is that for patients with chronic schizophrenia who need long-term antipsychotic treatment, especially postmenopausal women and patients with high prolactin levels or severe negative symptoms, clinicians should prioritize aripiprazole (when clinically appropriate) to reduce the risk of bone mass decline, and regularly monitor bone density and prolactin levels during treatment. At the same time, interventions such as increasing physical activity and improving nutritional status should be given to reduce the risk of bone health problems in these patients.

Data Sharing Statement

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1964. All procedures involving human subjects/patients were approved by the Ethics Committee of Beijing Changping Hospital of Integrated Chinese and Western Medicine, Beijing, China. The ethical approval number was YJKT-20250057. Before being recruited into the study, all the participants signed the informed consent form themselves. If the patient lack capacity

to provide informed consent, the patient's guardian should fully understand the research contents and then sign the informed consent form.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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