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Prevalence, risk factors and clinical characteristics of osteoporosis in Chinese inpatients with schizophrenia

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ABSTRACT

Patients with schizophrenia have a high prevalence of developing osteoporosis and osteoporosis-related fractures. We examined the prevalence of osteoporosis and its clinical correlates in Chinese patients with schizophrenia, which is not well-studied. A total of 199 inpatients (males/females = 132/67; average age: 54.5 ± 11.1 years) and 107 healthy controls (males/females = 22/85; average age: 41.7 ± 11.9 years) were recruited. Bone mineral density (BMD) was measured by ultrasonography of the calcaneus. The prevalence of osteoporosis and low BMD (osteoporosis and osteopenia) was 23.1% and 65.3% for the patient group, versus 7.5% and 39.3% for the control group (both $p < 0.001$). Further, the average BMD T-score in patients was significantly lower than in controls ($p < 0.05$). There was gender difference in the prevalence of low BMD conditions for the patients (males: 56.1% versus females: 76.1%; $p < 0.01$) as well as the BMD T-score ($p < 0.001$). Several risk factors correlated with the osteoporosis classification in the patient group: older age (58.9 ± 11.2 years vs. 53.3 ± 11.0 years), lower weight (63.7 ± 12.2 kg vs. 70.4 ± 15.2 kg) and body mass index (BMI) (22.8 ± 4.1 kg/m^2 vs. 24.2 ± 4.7 kg/m^2; all $p < 0.01$) than those without osteoporosis. Stepwise multiple logistic regression analysis indicated that age, weight and BMI remained significantly associated with osteoporosis. In addition, correlation analysis showed significant correlations between BMD T-score and the following parameters: gender, age and drug type (clozapine versus non-clozapine) (Bonferroni corrected p's < 0.05). Our results suggest a higher prevalence of osteoporosis and osteopenia in Chinese schizophrenic inpatients, with both the expected risk factors of gender and age, as well as drug type.

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1. Introduction

Osteoporosis is a degenerative disease where excessive osteoclastic activity or insufficient osteoblastic activity produces thinned and weaken bones, as indicated by metrics of bone mineral density (BMD); the disease results in an increased risk for fractures in general and unique predisposition to fragility fractures that are osteoporosis-specific, such as wrist or vertebral fractures (Stubbs et al., 2014; Gomez et al., 2016). Osteopenia is a precursor to this disease, where BMD is lower than expected for a given age, but no fracture has occurred or the BMD is <2.5 standard deviations below the mean. Osteoporosis is a major public health problem worldwide affecting about 200 million people and resulting in increased morbidity and mortality and decreased quality of life (Kanis, 2002; Kanis et al., 2013). The majority of the previous studies report that the incidence of reduced BMD was significantly higher in schizophrenia patients than that in healthy subjects (Halbreich et al., 1995; Bilici et al., 2002; Renn et al., 2009; Jung et al., 2011; van der Leeuw et al., 2013; Sugawara et al., 2012; Bulut et al., 2016). However, some studies have failed to show difference in BMD between schizophrenic patients and healthy controls, especially in first-episode psychosis or the early-stage schizophrenia patients (Doknic et al., 2011; Wang et al., 2014). Three recent meta-analyses have shown that schizophrenic patients do have significantly lower BMD than in healthy controls, especially at the lumbar spine and hip (Stubbs et al., 2014; Tseng et al., 2015; Gomez et al., 2016). Schizophrenic patients also have a higher prevalence of osteoporosis with associated fractures (Halbreich, 2007; Kishimoto et al., 2012; Tseng et al., 2015), confirmed by a recent meta-analysis (Stubbs et al., 2015).

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The underlying mechanisms for decreased BMD in schizophrenia are still unclear. The following factors may play an important role: 1) poor nutrition (Teasdale et al., 2017) and low vitamin D (Lally et al., 2016), antipsychotic induced hyperprolactinaemia (Lally et al., 2017), high levels of diabetes (Vancampfort et al., 2016) and low physical activity with high levels of sedentary behavior (Stubbs et al., 2016a; Stubbs et al., 2016b). The role of antipsychotics appears to be particularly important and osteoporosis has been demonstrated to be a significant late-stage side effect of these drugs (Crews and Howes, 2012; Jalbert et al., 2010; Wu et al., 2013; De Hert et al., 2016). Reduced BMD has been associated with antipsychotic-induced hyperprolactinaemia and/or secondary hypogonadism (Naidoo et al., 2003; Kinon et al., 2013; Wang et al., 2014; Lally et al., 2017). While most typical antipsychotics result in hyperprolactinemia, most atypical antipsychotics (excluding risperidone) do not (Kinon et al., 2003; Bushe and Shaw, 2007; Wang et al., 2014). Among prolactin-sparing (PS) antipsychotics (clozapine, olanzapine, quetiapine or aripiprazole), the effects of olanzapine on BMD have been studied with inconclusive results (Meaney and O'Keane, 2007; O'Keane, 2008; Okita et al., 2014; Chen et al., 2016). Only one previous study examined the effect of clozapine on BMD, showing that clozapine therapy was protective for reduced BMD in women with chronic schizophrenia compared to prolactin-raising (PR) antipsychotics – this was dose-dependent (Lin et al., 2012). Since clozapine is the most efficacious treatment for schizophrenia despite its notable side effects requiring significant monitoring already (Correll et al., 2009), clozapine's effect on BMD in schizophrenia merits further investigation.

Previous studies have reported variance in prevalence of reduced BMD and osteoporosis among ethnic populations (Jung et al., 2006). For example, on average Asians have a lower BMD when compared to other ethnic groups, (Jung et al., 2006, 2011) but within this broad category, only a few specific populations have been parsed out. A previous study revealed no significant difference in BMD between Chinese schizophrenic patients and healthy controls at pretreatment, but a significant difference after typical antipsychotic treatment (Wang et al., 2014). Interestingly, Lin et al. (2015) reported lower BMD in male than female patients in Chinese schizophrenia patients in Taiwan, with the other risk factors for low BMD differing between genders. Among postmenopausal women with schizophrenia, the prevalence of osteoporosis or osteopenia has recently been reported as 66.2% in postmenopausal women with schizophrenia; this study identified several demographic and clinical risk factors for decreased BMD (Liang et al., 2016). However, the risk factors and clinical correlations of decreased BMD and osteoporosis in Chinese schizophrenia patients are still inconclusive.

Numerous previous studies have examined reduced BMD in schizophrenia with mixed results. Most studies examining reduced BMD and osteoporosis in schizophrenia have focused on Caucasian patients, and only a few systematic studies have investigated the demographic and clinical correlates of decreased BMD and osteoporosis in Chinese schizophrenia patients – those that have reported inconsistent conclusions. Further, no study has examined the effect of clozapine on BMD in Chinese patients, despite clozapine being one of the most commonly used antipsychotic medications for the treatment of schizophrenia in China (Tang et al., 2008). The major aims of this study, therefore, were to investigate 1) whether BMD was significantly lower in schizophrenic patients compared to healthy controls in a Chinese Han population; 2) whether certain demographic and clinical characteristics were significantly associated with reduced BMD or osteoporosis in these patients; and 3) whether clozapine altered the prevalence of and risk factors for decreased BMD.

2. Methods

2.1. Design, setting and participants

This cross-sectional study was carried out in inpatient wards of Beijing Hui-Long-Guan Hospital, a Beijing City-owned psychiatric hospital, from June 1, 2014, to December 31, 2015.

We recruited patients meeting the following criteria: 1) 18–75 years old; 2) diagnosed with schizophrenia by two psychiatrists using the Chinese version of Structured Clinical Interview for DSM-IV (SCID); 3) having no other psychiatric diagnoses; 4) having the diagnosis for at least 2 years to meet the eligibility of chronicity; 5) not pregnant or lactating; 6) no other major medical conditions (e.g. infections, cancer) or central nervous system diseases. A total of 199 patients (132 male and 67 female) were included in our current study.

After hospital admission, all patients had a balanced diet with three meals daily and generally engaged in 1 h of physical exercise every day. Occasionally, they received some fruits or snacks as supplementation by their family members or friends.

107 control subjects (male/female = 22/85) were recruited from the local community in Beijing. Their current mental status and personal or family history of any mental disorder were evaluated by a research psychiatrist by unstructured clinical interviews. None of them displayed a personal or family history of psychiatric disorder.

For all subjects, a questionnaire survey was administered to collect general information, sociodemographic data, smoking behavior, and medical conditions by trained research staff, who were blind to the status of the subjects. A complete medical history, physical examination, and laboratory tests were obtained, and we excluded those subjects with test abnormalities or medical illnesses. None of them suffered from drug or alcohol abuse/dependence. All subjects were Han Chinese. After the study procedure was explained in details to all subjects, they signed the informed consent document. The Institutional Review Board of Beijing Hui-Long-Guan hospital approved our current study.

2.2. Measure of bone mineral density in patients and healthy controls

Using the 3.01 Sahara Clinical Bone Sonometer (Hologic), 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. 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 stiffness index (SI) was calculated by the following formula: $SI = (0.67 \times BUA + 0.28\ SOS) - 420$, which was reported as the QUS T-score; this indicates 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 (Collinge et al., 2010). QUS is a simple, easily transportable, radiation-free and comparatively inexpensive tool for evaluating BMD and osteoporosis (Collinge et al., 2010; Kinon et al., 2013).

We computed the T-score by subtracting the average BMD of healthy young adults from the measured BMD of the subject, which is the primary diagnostic value in older adults. We then compared this to the *Z*-score calculated using healthy age-matched reference BMD in young adults and children (Shepherd and Blake, 2007). Since the mean age of subjects in our current study was 54.5 years for patients and 41.7 years for controls, the T-score was used in this study.

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 $\geq$ 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).

2.3. Measurement of anthropometric variables

Body weight and height were measured in a standardized fashion, 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

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