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The risks of major osteoporotic fractures in patients with schizophrenia: A population-based 10-year follow-up study

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ABSTRACT

Objective: The aim of the study is to explore the incidence and the risks associated with major osteoporotic fractures, all-cause mortality with osteoporotic fractures and the effect of the psychiatric drug exposure in patients with schizophrenia during a 10-year follow-up period.
Methods: Two nationwide cohorts were selected from the Taiwan National Health Insurance Research Database (NHIRD) consisting of 30,335 patients with schizophrenia (age ≥ 40 years) and 121,340 age- and sex-matched control participants without schizophrenia. The psychiatric proportion of days covered (PDC) is an indicator of the intensity of drug exposure in patients with schizophrenia. The incidence and risk factors of major osteoporotic fractures were calculated for both cohorts. Additionally, the patient survival rate after major osteoporotic fractures was also calculated.
Results: During a 10-year follow-up period, 1677 (5.53%) schizophrenia and 4257 (3.51%) control subjects had major osteoporotic fractures ($P < 0.001$). The schizophrenia patients with a PDC > 0.1 showed a significantly higher incidence of major osteoporotic fractures than did the non-schizophrenia controls; however, those with a psychiatric PDC ≤ 0.1 did not. After adjustment, the psychiatric PDC was significantly and independently associated with the risk of major osteoporotic fractures except some medical morbidities but the schizophrenia diagnosis was not. In addition, among all 5934 patients with major osteoporotic fracture, the adjusted mortality hazard ratio for psychiatric PDC was 1.92 (95% CI = 1.63–2.26).
Conclusions: Patients with schizophrenia are at a higher risk for major osteoporotic fractures than the general population and also have a higher mortality rate due to major osteoporotic fractures. These findings may be caused by psychiatric drug use rather than schizophrenia, which suggests that directions can be taken in future studies.

1. Introduction

In the United States, approximately 2 million people per year suffer from osteoporotic fractures (Dempster, 2011), which leads to marked morbidity, disability, mortality, and socioeconomic burden (Sasser et al., 2005; Dempster, 2011). Approximately 81% of all fractures in women 50 years of age and older can be attributed to osteoporosis (Bessette et al., 2008). In Taiwan, the prevalence rates of osteoporosis in people 50 years of age and older were 23.9% in males and 38.3% in females (Lin and Pan, 2011). Osteoporosis is seldom recognized by doctors or patients during routine clinical care, making fractures the first noticeable sign of the disease in many cases (Fechtenbaum et al., 2005). Osteoporosis is a condition that increases the risk of hip fractures (Riggs and Melton, 1995). Osteoporotic fractures also occur in skeletal sites other than the hip, such as the forearm, humerus, ankle, and vertebrae (Tarantino et al., 2010). Osteoporotic fractures can also increase the risk of mortality (Center et al., 1999).

Many studies have suggested that schizophrenia is associated with decreased bone mineral density (Halbreich et al., 1995; Abraham et al., 2003), particularly in patients treated with antipsychotic drugs

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(Halbreich and Palter, 1996). Hyperprolactinemia is a side effect of many antipsychotic medications (Molitch, 2005), and this condition was found to be prevalent among patients with schizophrenia (Halbreich et al., 2003). Hyperprolactinemia has been well-documented to lead to low bone mineral density (Meaney et al., 2004), which is one of the risk factors for osteoporotic fractures. The hyperprolactinemia in psychiatric patients treated with psychotropic drugs is more likely a consequence of the drug's side effects rather than a consequence of schizophrenia itself (Haddad and Wieck, 2004). Most antipsychotic drugs cause hyperprolactinemia; furthermore, antipsychotics are the most common pharmacologic agents that cause hyperprolactinemia (Molitch, 2005). In addition to antipsychotics, many other psychiatric drugs used by schizophrenia patients, such as antidepressants (TCAs, MAO inhibitors, and SSRIs), alprazolam, and lithium, can also cause hyperprolactinemia (Madhusoodanan et al., 2010). In a case–control study, Howard et al. (2007) found that psychiatric drugs (neuroleptics, SSRIs, anticonvulsants, tricyclic antidepressants, and hypnotics) were independently associated with hip fractures; however, schizophrenia as a disease was not associated with hip fractures. In contrast to previous studies, some researchers have reported that schizophrenia treated with antipsychotics is not associated with osteoporosis (Lin et al., 2012) and that antipsychotic drugs did not cause bone fractures in their studied patient population (Stubbs et al., 2009).

Higher doses of potent antipsychotic drugs have been reported to be associated with increased rates of both hyperprolactinemia and bone mineral density loss (Meaney et al., 2004). However, due to the lack of direct evidence of antipsychotic-induced hyperprolactinemia, the World Health Organization has not included antipsychotic drugs in its list of prescribed medications associated with the development of osteoporosis. The psychiatric proportion of days covered (PDC) is an objective and validated measure for characterizing medication adherence in patients with schizophrenia (Sleath et al., 2010), as it is an indicator of the intensity of drug exposure. There are no systematic prospective long-term follow-up studies that explore the association between the PDC and major osteoporotic fractures in patients with schizophrenia. Therefore, we conducted a retrospective cohort study to explore the incidence, the risks associated with major osteoporotic fractures, the all-cause mortality with osteoporotic fractures and the effect of psychiatric drug exposure in schizophrenia during a 10-year follow-up period.

2. Methods

2.1. Database subjects

In 1995, Taiwan initiated a single-payer National Health Insurance (NHI) program. By 2007, more than 98% of Taiwan's population was enrolled in this program. This study utilized the National Health Insurance Research Database (NHIRD), which was published by the National Health Research Institute in Taiwan and covers data from the years 1999 to 2010. The diagnostic coding of the NHI program in Taiwan was performed according to the International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) diagnostic criteria. According to their website, the National Health Insurance Bureau of Taiwan randomly reviewed the charts of one per 100 ambulatory and one per 20 inpatient claim cases and interviewed patients to verify the accuracy of the diagnosis (2000).

In Taiwan, patients with schizophrenia can apply for catastrophic illness registration (CIR) cards, and they do not need to pay co-payments (Chou et al., 2011; Chou, Tsai, and Chou, 2013). Patients are required to have a conclusive diagnosis by a psychiatrist to apply for CIR cards from the National Health Insurance Bureau.

This study used 1999–2000 CIR cards to identify schizophrenia subjects (ICD-9-CM code 295). According to previous studies on osteoporotic fractures (Piscitelli et al., 2011; Rubin et al., 2013), only subjects older than 40 years of age were included. In addition, to decrease confounding error subjects who were previously diagnosed with fractures at any site (ICD-9 800–829, E887, and A-code A470–A476, A479) during the 1999–2000 period were excluded from the study. In the end, the authors identified 30,335 subjects with schizophrenia to fit the inclusive criteria.

From the remaining subjects included in the year 2000 administrative data, subjects who were previously diagnosed with fractures at any site during the 1999–2000 period or who developed schizophrenia between the year 2001 and 2010 were excluded. For each schizophrenia subject, four age- and gender-matched non-schizophrenia subjects were randomly extracted as a control cohort.

The PDC focuses on persistence or continuation at the time of prescribed treatment. It is defined as the total number of medication covered days divided by the number of days in a certain time period. Claims data, including refill dates, days of supply, dose, and frequency, are used to calculate the PDC (Sikka et al., 2005; Chou, Tsai, and Chou, 2013).

Many psychotropic drugs induce hyperprolactinemia (Madhusoodanan et al., 2010), which may lead to osteoporotic fracture. The PDC is an objective and validated measure for characterizing medication adherence in patients with schizophrenia (Sleath et al., 2010), as it is an indicator of the intensity of drug exposure. The psychiatric PDC was computed as the number of days during which psychotropic drugs were dispensed as a percentage of the total observation days in the 2001–2010 NHIRD (Hess et al., 2006). The total observation days are calculated from January 01, 2001 to the day that the subject withdrew from the insurance program, was lost to follow-up, died, the diagnosis of major osteoporotic fracture was made, or December 31, 2010. Prescriptions from both outpatient and inpatient clinics were included. Medication oversupply was truncated at 100% because this measure does not address the overuse of medications.

Details on comorbid medical disorders, including hypertension, cardiac arrhythmia, hyperlipidemia, obesity, diabetes mellitus, dementia, Parkinson's disease, depression, chronic kidney disease, menopause, cancer, thyrotoxicosis, and alcoholism, were extracted from the 1999–2000 NHIRD. All of the conditions were associated with osteoporotic fractures (Lai et al., 2013).

The participants of the National Health Insurance in Taiwan were classified into four subgroups, according to socioeconomic status: EC 1 (highest socioeconomic status), EC 2, EC 3, and EC 4 (lowest socioeconomic status) (Chou et al., 2011; Tsai et al., 2012; Chou, Tsai, and Chou, 2013). The authors also used EC as an approximate measure of socioeconomic status, which is an important risk factor for osteoporotic fractures and case fatality rate (Meadows et al., 2012).

The urbanization level of the patient's residence is also associated with fractures and therefore was included in our analysis (Kruger et al., 2011). The authors categorized the level of urbanization into three subgroups: urban (urbanization level 1–2), suburban (urbanization level 3–4) and rural (urbanization level 5–7) (Chou, Tsai, and Chou, 2013).

Because all identifying personal information was removed from the secondary files before analysis, the review board for this study waived the requirement of written informed consent from the patients involved in this study. This study was initiated after approval by the Institutional Review Board (IRB) at the Municipal Kaohsiung Kai-Syuan Psychiatric Hospital (KSPH 102031).

2.2. Measurements

The key dependent variables in this study were the incidence of major osteoporotic fracture and the survival time of major osteoporotic fracture patients. The diagnosis of a major osteoporotic fracture includes fracture of the spine (ICD-9 805 and 806), hip (ICD-9 820), humerus (ICD-9 812), forearm (ICD-9 813), or wrist (ICD-9 814), as defined by the World Health Organization fracture risk assessment tool (FRAX) (Kanis et al., 2011; Lai et al., 2013). Both the schizophrenia and non-schizophrenia groups were followed from January 1, 2001 to December 31, 2010 to determine the fracture incidence, and subjects were