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The impact of prolactin-raising antipsychotics on bone mineral density in patients with schizophrenia: Findings from a longitudinal observational cohort

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ABSTRACT

To examine the effect of prolactin-raising antipsychotics on bone mineral density (BMD), data of 164 schizophrenia patients who received ≥2 dual-energy x-ray absorptiometry scans were analyzed (49.3% men; mean ± SD age: 58.5 ± 11.0 years; duration of treatment: 26.7 ± 13.8 years). Patients were divided into a prolactin-raising antipsychotic (n = 141) or prolactin-sparing (n = 23) group, and time x group interaction was examined using mixed effect model. Although the BMD difference did not reach significance over 3.4 ± 1.6 years, a significant antipsychotic-class vs. time interaction was found (p = 0.011), indicating a negative impact of prolactin-raising antipsychotics on BMD. Large-scale, randomized-controlled data are required to replicate and extend these findings.

1. Introduction

While lower bone mineral density (BMD) among patients with schizophrenia was reported for the first time in 1980 (Baastrup et al., 1980), insufficient attention had been paid to this phenomenon until a decade ago. However since then, a growing number of reports have focused on this topic (Abraham et al., 2003a; Becker et al., 2003; Howes et al., 2005; Lehman and Meyer, 2005), and a majority of them reported lower BMD in this population compared to healthy controls (Kishimoto et al., 2005; Renn et al., 2009; Rey-Sánchez et al., 2009; Jung et al., 2011). Osteoporosis can cause spinal fractures and other complications (Lindsay et al., 2001), and not only lowers activities of daily life, but is also associated with increased mortality (Center et al., 1999; Bliuc et al., 2009).

Hyperprolactinemia caused by antipsychotic treatment may negatively impact on BMD. Sufficiently elevated serum prolactin can suppress the secretion of gonadotropin-releasing hormone from the hypothalamus, which in turn results in a reduced secretion of luteinizing hormone and follicle stimulating hormone from the pituitary gland. These changes in sex hormone levels can lead to abnormal bone metabolism (Kishimoto et al., 2008).

However, findings on the impact of hyperprolactinemia on BMD are still inconsistent in the literature, possibly due to methodological limitations, such as predominantly cross-sectional study designs and small sample sizes (Kishimoto et al., 2012). To date, there are only two studies that prospectively examined this issue (Abraham et al., 2003b; Meaney and O'Keane, 2007). While these two studies found a negative effect of hyperprolactinemia on bone turnover markers or BMD, the sample sizes were very small (14 and 38 patients, respectively) and the follow-up duration was only one year.

In this study, we present data from a larger prospective observational study, which followed patients for up to 5 years, examining the effect of prolactin-raising compared to prolactin-sparing antipsychotics on BMD alongside with other risk factors.

2. Method

2.1. Subjects

BMD measurement data that were routinely obtained at Ohizumi Hospital, Tokyo, Japan, from February, 2005 and January 13, 2011, were systematically reviewed. In order to examine longitudinal changes

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in patients with schizophrenia, we retrieved available data of all patients with schizophrenia (the International Classification of Diseases, the 10th edition; ICD-10) who had received two or more measurements during the study period. We excluded patients from the analysis whose charts contained insufficient information. Patients with limited physical activity such as wheel chair-bound or bed-ridden, were also excluded considering a lack of exercise has significant impact on BMD and are not suited for the specific purpose of this study; i.e. to examine prolactin effect on BMD. At this hospital, inpatients and outpatients were encouraged to receive BMD measurement as part of regular clinical care through hospital brochures and posters. In addition, inpatients ≥40 years old were also recommended by their treating psychiatrists in person to receive BMD measurement during their stay. This data file study received approval of the Ethics Committee of the Ohizumi Hospital, which granted a waiver for informed consent.

2.2. Data collection

The following information was retrieved from the patients' charts: psychiatric diagnoses based on the ICD-10 criteria, age, sex, height, weight, total protein level in plasma, smoking habit, age of onset of illness, duration of psychiatric treatment and prescribed medications at the time of the first BMD assessment. Inpatients received monthly blood draws during the hospitalization, and data closest to the BMD measurement date were extracted.

Patients were classified into two groups according to the antipsychotic drugs prescribed at baseline: prolactin-raising and prolactin-sparing antipsychotic groups (Byerly et al., 2007). When the subjects were on two or more antipsychotics, they were classified into the prolactin-raising antipsychotic group if any of the antipsychotic was prolactin-raising (Montgomery et al., 2004). However, if any of the medications was aripiprazole, they were sorted into the prolactin-sparing group (Shim et al., 2007; Byerly et al., 2009). Prolactin-raising antipsychotics included all first-generation antipsychotics, risperidone and blonanserine (a serotonin-dopamine antagonist) (Deeks and Keating, 2010); prolactin-sparing antipsychotics included aripiprazole, olanzapine, perospirone (a serotonin-dopamine antagonist) (Togo et al., 2003) and quetiapine. Doses of antipsychotics were expressed as chlorpromazine equivalents, using established conversion factors (Woods, 2003; Lehman et al., 2004; Inagaki and Inada, 2008).

2.3. BMD measurement

BMD was measured using dual-energy x-ray absorptiometry (DEXA) (Aloka Dicroma scan DCS-600EX-3, Aloka Co., Ltd., Tokyo, Japan) at the distal one-third portion of the radius of the arm contralateral to the dominant arm of the subject. BMD was expressed as t-score and z-score that are defined as follows:

t = (subject's BMD - young adult mean)/young adult SD.
z = (subject's BMD - mean BMD of the age and sex-matched group)/SD of the age and sex-matched group.

Therefore, a t-score expresses subject's BMD compared to the optimal peak BMD and was used for diagnosis of osteoporosis (i.e. t- ≤ 2.5) according to the criteria by the World Health Organization (2003). On the other hand, since a z-score minimizes the effect of sex and age, it was used for group comparison.

2.4. Statistical analyses

Distributions of all variables were inspected using histograms, q-q plots and Shapiro–Wilks tests before conducting statistical analyses. Differences in patient characteristics between groups were examined using chi-square analysis for categorical variables and ANOVA for continuous variables. The first DEXA scan during the study period was regarded as baseline data, and DEXA scans at 12, 24, 36, 48 and 60 months were used as follow-up data. For each follow-up time point, we used a ±6 month window. We assumed that missing data were missing at random. The primary analysis was performed using a mixed models approach with a random intercept that accounted for correlation across time points. Unstructured covariance was used to fit the covariance structure in the mixed models analysis. The difference in the time course between PRL-raising and PRL-sparing groups was assessed using a time × group interaction term in the mixed models adjusted by body mass index, smoking (yes/no), serum total protein, and antipsychotic polypharmacy. Multiple imputations using a maximum likelihood approach with the Expectation–Maximization algorithm was used to account for missing values. Statistical analyses were carried out using JMP 5.0.1, SAS Institute Inc. and PROC MIXED, MI and MIANALYZE in SAS version 9.2. All analyses were two-sided with alpha set at 0.05.

3. Results

3.1. Study sample

Three-hundred-four patients with schizophrenia received DEXA scans during the target period. Sixty patients were excluded due to limited physical activity or insufficient information in the charts. Out of the remaining 244 patients, 164 patients received DEXA scans at least twice and were included in the analysis.

3.2. Demographic characteristics and baseline BMD

Demographic characteristics of the patients are shown in Table 1; there were no significant differences between prolactin-raising ($n = 141$) and prolactin-sparing ($n = 23$) groups, except for greater antipsychotic polypharmacy rate in the prolactin-raising group ($p < 0.0001$) and greater concomitant antidepressant use in the prolactin-sparing group ($p = 0.0097$). No significant BMD difference was found between the two groups at baseline ($p = 0.42$). Fifty out of 164 patients (30.5%) were diagnosed as osteoporosis based on t-score. The osteoporotic patients were more female (67.7% vs. 32.3%, $p = 0.03$) and older (63.9 ± 9.2 vs. 55.4 ± 10.6, $p < 0.001$) compared to the non-osteoporotic patients.

3.3. BMD over time

During a mean follow-up period of 3.4 ± 1.6 years, there was a difference in the time course of BMD between the PRL-raising and PRL-sparing groups, indicated by a significant time vs. group interaction term in the mixed model analysis ($p = 0.011$). However, the BMD z-scores at each time point (i.e., main effects) were not significantly different between the two groups (Fig. 1).

4. Discussion

Our longitudinal observational data demonstrated that patients on prolactin-raising antipsychotics were significantly different from those on prolactin-sparing antipsychotics regarding BMD change over time. As the plots indicated, the z-scores of prolactin-sparing group increased over time (i.e., BMD became close to the average of healthy population), whereas z-scores of the prolactin-raising group did not change over time (i.e., BMD remained lower than the reference data). Although it should be noted that BMDs of the two groups failed to reach any statistically significant difference at each individual time point across the five years of follow-up, the data suggest a potentially negative impact of prolactin-raising antipsychotics on BMD. Moreover, female and old age were associated with osteoporosis in our population. These findings