Bone Loss Associated with Hyperprolactinemia in Patients with Schizophrenia: Are There Gender Differences?

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Abstract

Background: Elevated prolactin (hyperprolactinemia) has been commonly reported during treatment with some antipsychotic drugs. A decrease in bone mineral density (BMD) may be related to elevated prolactin. The objective of this study was to determine the prevalence of low BMD in patients with schizophrenia treated with conventional antipsychotics or risperidone and to evaluate any potential relationship with treatment. **Methods:** A large-scale, cross-sectional secondary analysis was performed to determine low BMD in schizophrenia patients (n=402) treated with conventional antipsychotics or risperidone for at least three months prior to study entry. BMD was determined by ultrasonography of the calcaneus. The potential effect of age, elevated prolactin, and duration of antipsychotic drug treatment on BMD was evaluated. Bone metabolism measures were determined and the potential effect of elevated prolactin and sex hormones on bone metabolism measures was also evaluated. Regression analysis was used for all the above analyses. **Results:** Low BMD was observed in about 1 in 4 female patients and 1 in 3 male patients. A negative correlation between T-score (BMD measure) and prolactin levels was found in male patients after controlling for age (p=0.05) and this correlation was not observed in female patients. Controlling for age, elevated prolactin was associated with elevated bone formation marker (osteocalcin) in both genders (female: p=0.03; male: p=0.05) and there was no significant correlation between change in T-scores and duration of antipsychotic drug for either gender. Total testosterone levels were negatively correlated with bone resorption marker (N-telopeptide) in men (p=0.04). **Conclusions:** Contrary to the trend in the general population with osteopenia, hyperprolactinemia during treatment with antipsychotic drugs may be associated with a greater prevalence of low bone mass in men compared to women. Elevated prolactin may have a direct effect on the bone, increasing bone turnover in patients of both genders, while hypogonadism may be associated with elevated prolactin in male patients only. Decreased testosterone levels due to hypogonadism in men may lead to increased bone resorption and subsequent low BMD.

Key Words: Bone Mineral Density, Schizophrenia, Antipsychotic Drugs, Gender Differences, Hyperprolactinemia

Introduction

An estimated 10 million Americans have osteoporosis and an additional 18 million have low bone mineral density (BMD; or osteopenia), and treatment of osteoporotic fractures accounts for $10 billion to $15 billion annually in the United States (1). Primary osteoporosis often follows menopause in women and occurs later in life in men. In the general population, the probability that a 50-year-old Caucasian female will have a hip fracture is 14% (female of African descent: 6%), while the probability for a 50-year-old Caucasian male is 5–6% (male of African descent: 3%) (1). Although age-related osteoporosis is the most common reason for bone fracture, there are several secondary causes of osteoporosis, including hyperprolactinemia (2, 3).

Prolactin elevation (hyperprolactinemia) has been commonly reported during treatment with antipsychotic medications and can have serious clinical consequences. Since conventional (typical) antipsychotic agents are nonselective in blocking dopamine pathways, blockade of the mesolim-

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Clinical Implications

In this large, cross-sectional study represented by both gender patients with schizophrenia, gender differences were observed in the prevalence of low bone mineral density (BMD) in patients treated with conventional antipsychotics or the atypical antipsychotic risperidone. Contrary to the general trend in which women are at a higher risk of osteopenia compared to men, hyperprolactinemia during treatment with antipsychotic drugs may be associated with a greater prevalence of low bone mass in men compared to women. Elevated prolactin may have a direct effect on the bone, increasing bone turnover in patients of both genders, while hypogonadism may be associated with elevated prolactin in male patients only. Hyperprolactinemia in men may result in low bone density due to an increase in bone resorption rate mediated by decreased testosterone levels. The negative association found between N-telopeptide and testosterone in men suggests that low testosterone is accompanied by high telopeptide, a marker for increased bone resorption. Hyperprolactinemia in women may result in increased bone turnover, yet a decreased prevalence of low BMD compared to men. This may be due to hypogonadism associated with elevated prolactin not applicable in women. Controlling for age, there was no significant correlation between change in T-score and duration of antipsychotic treatment for either gender. Findings from this study underscore the need to evaluate bone health in both men and women treated with antipsychotic drugs that have the propensity to raise prolactin levels.

bic and mesocortical dopaminergic pathways is attributed to their clinical efficacy, blockade of nigrostiatal dopamine pathway to their extrapyramidal adverse events, and blockade of dopamine receptors in the tuberoinfundibular system to hyperprolactinemia (4). Atypical antipsychotics differ in the risk of hyperprolactinemia possibly due to the sparing action of some atypical drugs to dopamine blockade within the brain's tuberoinfundibular tract (5, 6). Elevated prolactin levels can interfere with the functioning of reproductive, endocrine, and metabolic systems (7). Sexual dysfunction may be related to elevated prolactin levels inhibiting the release of hypothalamic gonadotropin-releasing hormone, which leads to reduced testosterone and estrogen production. Prolonged estrogen deficiency in women and testosterone deficiency in men may result in decreased BMD (4, 8-10). A review of data on BMD in male patients with schizophrenia by Meyer and Lehman shows that low bone mass in men may be a highly prevalent but significantly underdiagnosed medical condition (10).

Elevated prolactin can also affect bone health independent of sex steroid hormones (11, 12). Serum and urinary markers for bone formation and resorption have been developed and may be applied to monitor prolactin response and its potential effect on BMD (13). The relative balance between bone formation and resorption can be assessed by following alkaline phosphatase and osteocalcin as measures of bone formation and N-telopeptide as a measure of bone resorption. Evaluating any potential relationship between antipsychotic drug treatment and decreased BMD is important and may lead to development of new treatment modalities. In a large scale naturalistic study of patients with schizophrenia (n=402), we demonstrated the prevalence of elevated prolactin in patients treated with conventional antipsychotic drugs and risperidone (14) and the association of sexual dysfunction and elevated prolactin (15). The objectives of the current analyses are to: 1) determine the prevalence of low BMD in patients with schizophrenia treated with conventional antipsychotics or the atypical antipsychotic risperidone in a large cohort (n=402); 2) evaluate any potential relationship between antipsychotic drug treatment and decreased BMD involving elevated prolactin, sex hormones, and bone markers; and, 3) determine the potential effect of duration of antipsychotic treatment on BMD.

Methods

Study Design

This was a post hoc analysis of a large, open-label, cross-sectional trial of patients with schizophrenia who were treated with conventional antipsychotics or the atypical antipsychotic risperidone (14). The trial included 402 inpatients and outpatients from routine clinical settings meeting diagnostic criteria for schizophrenia, schizoaffective disorder, or schizophreniform disorder, according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*. Patients between 18 and 70 years of age were required a priori to have been treated with a conventional antipsychotic drug or risperidone for a minimum of three months prior to study entry. Neither patients nor physicians had any prior knowledge of serum prolactin levels or any potentially associated adverse events. Key exclusion criteria included concomitant medications known to elevate prolactin, pregnancy, breastfeeding, thyroid or pituitary gland diseases, *DSM-IV*-defined substance abuse or dependency, and sex hormone therapy. Additional details are available in the primary report of the study (14). The study protocols and informed consent documents were approved by the Institutional Review Board at each participating site, and the studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. All patients pro-

vided written informed consent consistent with all local and regional regulatory requirements prior to undergoing any study procedure or receiving any study treatment.

Eligible patients entered the one-day study conducted at 27 centers in the United States from September 1998 through May 2000. Patients arrived at the study center soon after rising in the morning, having abstained from food and medication since midnight. A mean serum prolactin level was determined from the early morning blood sample and a second blood sample drawn after 3–4 hours, representing a midway between the peak and trough variability in patient prolactin levels. Hyperprolactinemia was defined as any mean value above the upper limit of normal values (18.8 ng/mL or 0.8 nmol/mL for males, and 24.2 ng/mL or 1.05 nmol/mL for females) (14).

Bone mineral density (g/cm^2) was determined by ultrasonography of the calcaneus using the Sahara Clinical Bone Sonometer (Hologic). Although the established diagnostic test to assess BMD and osteoporosis in the general population is dual-energy x-ray absorptiometry (DXA), quantitative ultrasound (QUS) is a radiation-free alternative to DXA for evaluating osteoporosis risk and is more mobile, less expensive, and easy to use (16). In addition, QUS may provide information concerning the structural organization of bone beyond that assessed by DXA (17). Several longitudinal studies have shown that heel QUS is as effective as DXA in predicting hip fractures (18-20) and heel QUS is a validated method in the diagnosis of metabolic bone diseases (21, 22).

The T-score expresses a patient's BMD as the difference between the measured BMD and the mean BMD for a healthy young adult (23). The result is reported in units of the young adult population standard deviation (SD). The World Health Organization (WHO) defines normal BMD as a T-score that is within 1 SD of a normal young adult; that is, a T-score of -1.0 or higher (24). A T-score between -1 and -2.5 indicates low BMD (osteopenia) and a T-score of -2.5 or less indicates osteoporosis (24).

The Z-score expresses a patient's BMD by using healthy age-matched reference BMD (23). While the T-score is the primary diagnostic value in older adults, the Z-score is primarily used in young adults and children (23). Since the average age of patients in this study was 40.8 years in men and 44.5 years in women (see Table 1), the T-score was determined.

Bone metabolism was assessed by serum levels of bone-specific alkaline phosphatase, osteocalcin, and N-telopeptide. To study the association of sex hormonal levels with BMD, serum levels of estradiol and total and free testosterone were also determined. Menopausal status of female patients was determined using a priori clinical criteria that included postmenopausal women as those ≥40 years old without a period for two years accompanied by several months of hot flashes on a daily basis, or both ovaries removed, or >60 years old with hysterectomy.

Assay Methodology

Blood samples were shipped at ambient temperature on the day of collection and assayed by Covance Central Laboratory (Indianapolis, IN). Prolactin was determined by Microparticle Enzyme Immunoassay (sensitivity: 0.60

Table 1 Patient and Disease Characteristics

	Males (N=255)	Females (N=147)
Age, years (mean±SD)	**40.8±10.0**	**44.5±11.4**
Race, n (%)		
Caucasian	124 (48.6)	62 (42.2)
African descent	96 (37.6)	68 (46.2)
Other	35 (13.7)	17 (11.6)
Diagnosis (%)		
Schizophrenia	85.5	76.2
Schizoaffective	14.5	23.8
Length of illness (years±SD)	**17.2±9.7**	**18.7±11.3**
Menopausal status, n (%)		
Premenopausal		90 (61.2)
Postmenopausal		51 (34.7)
Perimenopausal/unknown status		6 (4)
Drug n/mean dose, mg/day		
Risperidone	84/5.2	42/4.7
Conventional, oral		
Chloropromazine	7/157.1	3/266.7
Fluphenazine	11/21.3	12/13.1
Haloperidol	28/14.3	16/8.7
Loxapine	4/86.3	3/41.7
Mesoridazine	3/166.7	2/27.5
Molindone	1/125.0	0
Perphenazine	5/8.4	9/14.4
Pimozide	1/4.0	0
Thioridazine hydrochloride	14/294.6	11/295.5
Tiotixene	10/21.5	5/8.0
Trifluoperazine	3/23.3	5/14.4
Conventional, depot		
Fluphenazine decanoate	43/74.4	18/60.9
Haloperidol decanoate	41/138.5	20/133.5

N=number of patients; n=number in group; SD=standard deviation

ng/mL; intra-assay coefficients of variation [CV]: 3.2–3.6%; inter-assay CV: 4.5–5.2%). Estradiol was measured using the double-antibody radioimmunoassay procedure (sensitivity: 1.4 ng/mL; intra-assay CV: 6.5%; inter-assay CV: 7.6%). Testosterone levels were measured using Coat-A-Count solid phase radioimmunoassay procedure (sensitivity: 8.0 ng/dL; intra-assay CV: 11.2%; inter-assay CV: 11.0%). Serum osteocalcin was determined using the OSTEO-RIACT kit with a double-antibody technique (intra-assay CV: 3.8–3.9%; inter-assay CV: 4.5–5.2%). Serum bone-specific alkaline phosphatase was measured using the Tandem-R Ostase two-site immunoradiometric assay (sensitivity: 2.0 ng/mL; intra-assay CV: 3.7–6.7%; inter-assay CV: 7.0–9.1%). The urinary concentration of N-terminal telopeptide of type I collagen (NTx) was measured by an enzyme-linked immunosorbent assay (ELISA). Urinary determinations were expressed in relation to creatinine excretion and the intra- and inter-assay CVs were 5–8% and 7–10%, respectively.

Statistical Methods

The potential effect of age, duration of drug treatment, and elevated prolactin on T-scores was determined by linear regression analysis. The combined effect of age and elevated prolactin on T-scores and bone formation measure (osteocalcin) was determined using multiple regression analysis. The association of T-score with bone markers was tested using the Pearson's correlation test. The effect of estradiol, total and free testosterones on bone markers, and T-score was assessed using linear regression analysis. T-score and bone markers for premenopausal female patients with hyperprolactinemia and amenorrhea were compared with patients having normal prolactin and menstrual activities using analysis of variance (ANOVA). All statistical tests were based on a two-sided significance level of 0.05.

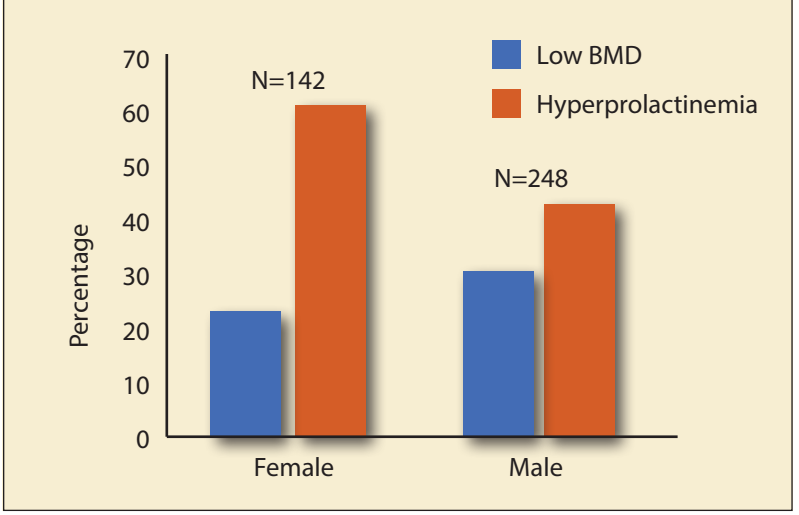
Results

Patient demographics and disease characteristics are summarized by gender in Table 1, along with the type of drug and dose used in the treatment. Mean age was 40.8 (±10.0) years for males and 44.5 (±11.4) years for females. Approximately one-third of patients were on risperidone treatment and the remaining two-thirds were on conventional antipsychotics. The average duration of treatment with all drugs was ≥8±5.8 years (data not shown). Among the female patients, 61% were premenopausal, 35% were postmenopausal, and 4% were perimenopausal or of unknown menopausal status.

Prevalence of Low BMD

The percentage of patients (by gender) showing low BMD (T-score <-1) is compared with hyperprolactinemia data in Figure 1. While 43% of male patients (n=248) had elevated prolactin (mean=20.2±14.6 ng/mL), 31% (about 1 in 3) had low BMD (mean T-score=-0.3±1.2; osteopenia, T-score <-1 to -2.5, n=70; osteoporosis, T-score <-2.5, n=7). In comparison, a higher percentage (61%) of female patients (n=142) had hyperprolactinemia (mean=44.1±36.0 ng/mL), and only 23% (about 1 in 4) had low BMD (mean T-score=-0.0±1.2; osteopenia, T-score <-1 to -2.5, n=32; osteoporosis, T-score <-2.5, n=1).

Figure 1 **Prevalence of Hyperprolactinemia and Low Bone Mineral Density (T-Score <-1) in Patients Treated with Conventional or the Atypical Antipsychotic Risperidone**



BMD=bone mineral density

Table 2 Association of Sex Hormone with Bone Metabolism Measures and BMD

	Premenopausal Female Patients	Postmenopausal Female Patients	Male Patients
Total testosterone—bone-specific alkaline phosphatase	√ (positive, p=0.05)	√ (positive, p=0.04)	x
Total testosterone—N-telopeptide	x	√ (positive, p=0.007)	√ (negative, p=0.04)
Total testosterone—osteocalcin	x	x	x
Total testosterone—T-score	x	√ (positive, p=0.005)	x
Free testosterone—bone metabolism measures	x	x	x
Estradiol—T-score	x	x	x
Estradiol—bone metabolism measures	x	x	x

x=no relationship observed; √=relationship observed

In the primary manuscript for this study, we reported a higher prevalence of hyperprolactinemia in risperidone-treated patients compared to conventional antipsychotic drug-treated patients (14). In the current study, prevalence of low BMD was not significantly different in risperidone-treated versus conventional antipsychotic drug-treated patients (risperidone: n=123, low BMD=30.9%, mean T-score=-0.16±1.35; conventional drugs: n=267, low BMD=27.0%, mean T-score=-0.2±1.2).

Since BMD in the general population is found to decrease with age (8), to determine the effect of elevated prolactin on BMD the effect of age on BMD (T-scores) was first determined, followed by the combined effect of age and prolactin on BMD. A significant inverse relationship was observed between age and BMD in both male ($p<0.007$) and female ($p<0.001$) patients. Controlling for age, a decrease in T-score with increase in prolactin was observed in male patients only ($p=0.05$).

Effect of Elevated Prolactin on Bone Formation Measure

The combined effect of age and elevated prolactin on serum osteocalcin (bone formation measure) in male and female patients was studied. Controlling for age, elevated prolactin was associated with elevated osteocalcin in both genders (male: $p=0.05$; female: $p=0.03$). Controlling for prolactin level, osteocalcin levels increased with age in women ($p=0.003$) and decreased with age in men ($p=0.0001$).

Correlation Analysis between BMD (T-Score) and Bone Markers

Pearson's product-correlation analysis of T-score with bone formation (osteocalcin and alkaline phosphatase) and bone resorption (N-telopeptide) measures is shown in Table 2. Consistent with the literature (25), a small negative correlation was observed between T-score and bone formation measures (osteocalcin and bone-specific alkaline phosphatase) and positive correlations between the bone markers (osteocalcin, bone-specific alkaline phosphatase, and N-telopeptide). All p-values for the above correlations were found to be significant (data not included).

Effect of Sex Hormones on Bone Markers and BMD (T-Score)

The relationship between sex hormones and bone metabolism measures was analyzed and is shown in Table 2. There were gender differences in the association of testosterone levels with bone markers and T-score. Total testosterone correlated negatively with N-telopeptide in male patients ($p=0.04$) and correlated positively in postmenopausal female patients ($p=0.007$). Total testosterone was positively correlated with bone-specific alkaline phosphatase in postmenopausal ($p=0.04$) and premenopausal ($p=0.05$) women and had no correlation in men. Total testosterone was positively correlated with T-score in postmenopausal women ($p=0.005$) and had no correlation in premenopausal women or men.

Potential Effect of Duration of Treatment on BMD

The potential effect of duration of total lifetime treatment of all antipsychotic drugs on BMD was assessed. Controlling for age, there was no significant correlation between duration of antipsychotic drug treatment and T-scores for either gender.

Discussion

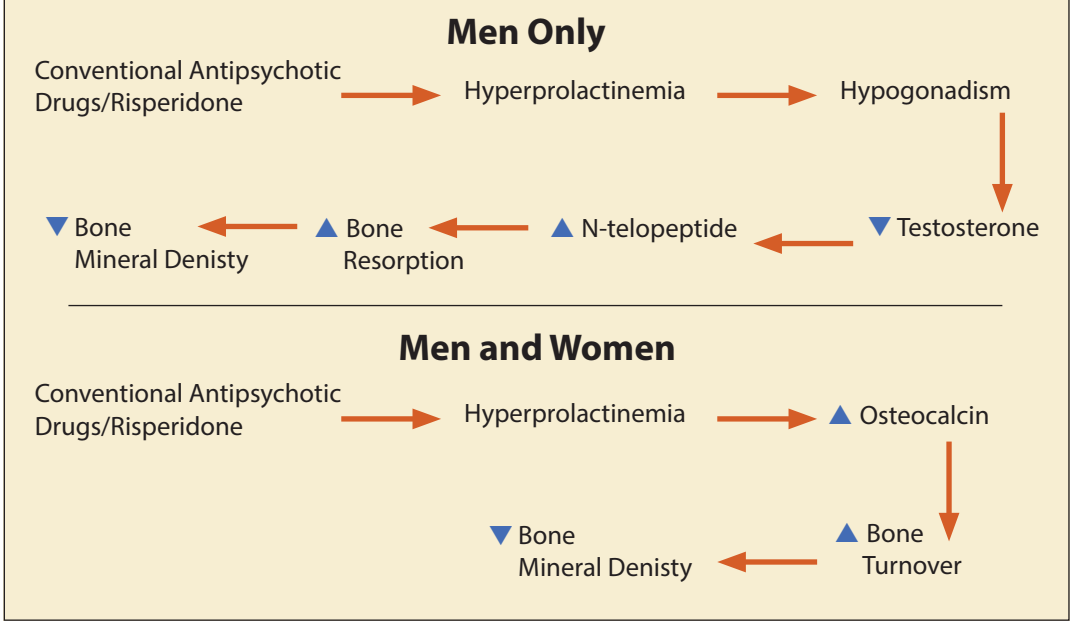
Gender differences were observed in the prevalence of low BMD in patients with schizophrenia treated with conventional antipsychotic drugs or risperidone. Although female patients showed a higher incidence of elevated prolactin compared to male patients (females: 61%; males: 43%), bone loss was more prevalent in men compared to women (females: 23%; males: 31%). Controlling for age, elevated prolactin levels were significantly associated with lower T-score (p=0.05) for male patients but not for female patients. This finding is consistent with several literature reports. Halbreich et al. report that 72–90% of male patients with major depressive disorder or schizophrenia treated with antidepressants or neuroleptic agents had low BMD depending on the measurement site, while only 9–41% of women had low BMD (26). Male patients showed a negative correlation between serum prolactin and BMD at the lumbar sites and this correlation was not observed in female patients. Meany et al. found in 55 patients with schizophrenia taking prolactin-raising antipsychotics for >10 years age-related reduced BMD in 57% of male patients compared to 32% of female patients (27).

It is well documented that treatment emergent hyperprolactinemia may be associated with hypogonadism leading to decreased BMD (29-31). This hypothesis is based on the clinical observation of osteopenia in men with hypogonadism (32). In an earlier report, we noted negative correlations between prolactin levels and total and free serum testosterone in men (correlation coefficient: -0.22 and -0.28; p=0.0003 and p=0.0001, respectively) (15). Data from this study show total testosterone negatively correlated with N-telopeptide in male patients. This suggests that lower testosterone levels associated with hyperprolactinemia may increase bone resorption rate leading to low BMD in male patients. The suggested pathway to low bone density associated with hyperprolactinemia in men is depicted in Figure 2. Meaney et al. report a low BMD associated with low free testosterone index values in a male group (27). These results support hypogonadism associated with hyperprolactinemia in male patients with schizophrenia.

Contributing Factors to Bone Loss Associated with Hyperprolactinemia in Women

Higher prevalence and severity of hyperprolactinemia in women compared to men is well documented in the literature (14, 33, 34). A gender difference in the regulation of dopamine D2 receptor system has been reported in the literature (35). However, the lack of correlation between T-score and elevated prolactin in women is an interesting observation also noted in several other studies. Schlechte et al. found no association between elevated prolactin levels and

Figure 2 Possible Pathways to Low Bone Mineral Density in Men and Women Treated with Antipsychotics



low BMD in 110 healthy women with hyperprolactinemia (29). Abraham et al. report that female schizophrenia patients (n=14) treated with risperidone for twelve months who experienced elevated prolactin failed to show an associated bone loss (36). Several studies of bone loss in hyperprolactinemic women have found reduced BMD associated with estrogen deficiency and not with prolactin elevation (29, 37, 38).

Two suggested pathways for bone loss associated with hyperprolactinemia are: 1) hyperprolactinemia-induced hypogonadism (39) and 2) direct effect of prolactin on bone from animal studies (11, 12). Elevated prolactin may have a direct effect on bone. Elevated markers of bone turnover have been associated with elevated prolactin (36). Patients with increased bone turnover markers lose bone at a faster rate than patients with normal or low bone turnover markers (40). In the current study, elevated levels of osteocalcin were observed with elevated levels of prolactin in patients of both genders. A moderate positive correlation between bone formation markers and bone resorption marker was observed, consistent with the findings of Lofmann et al. (25). When considered together, the above data indicate high bone turnover and associated bone loss with elevated prolactin in both genders. The bone loss in women may be associated with a direct effect of elevated prolactin on bone, resulting in increased bone turnover as shown in Figure 2.

Hyperprolactinemia–Decreased Estrogen–Low BMD Path not Observed in Women

While elevated osteocalcin was observed in hyperprolactinemic men and women patients, low BMD was less prevalent in women compared to men. There may be protecting factors operating in women that inhibit bone loss despite hyperprolactinemia and increased bone turnover. Estrogen is a major bone regulatory factor. Estrogen therapy can delay osteoporosis in postmenopausal women (41). Estrogen receptors exist on bone formation cells and estrogen also inhibits bone resorption, resulting in a net effect of bone formation and a decrease in bone resorption.

The effect of estradiol on T-score or bone markers in pre- and postmenopausal women was not significant in this study. In an earlier report, we noted 31.6% of reproductive hyperprolactinemic women having decreased estradiol (14). However, we found no significant association between prolactin and estradiol (15). The data considered together may suggest that estradiol levels are not affected by elevated prolactin in women. Hypogonadism associated with hyperprolactinemia may not be applicable in women. Canuso et al. report similar rates of menstrual dysfunction and ovarian hormone values for hyperprolactinemic and normoprolactinemic women with schizophrenia (42). In a comparative study of 72 premenopausal women with schizophrenia on antipsychotic medications and 71 age-matched healthy controls, Bergemann et al. report high bone turnover but normal bone BMD in the schizophrenia group (43). In a one-year prospective study of female patients with schizophrenia, Abraham et al. did not find any significant difference in bone loss in patients with or without hyperprolactinemia (36). Higher rates of bone formation and resorption were associated with elevated prolactin (significant group-by-time interactions were observed for osteocalcin, bone formation marker and N-telopeptide, and bone resorption marker). However, few other studies suggest hypogonadism associated with hyperprolactinemia in female schizophrenia patients (44, 45).

Based on the findings in this study, it is not clear why total testosterone levels correlate negatively with N-telopeptide in men, correlate positively in postmenopausal women, and show no correlation in premenopausal women.

Gender Differences in Bone Loss Associated with Hyperprolactinemia During Antipsychotic Treatment

Gender differences in the diagnosis and treatment of schizophrenia is well documented in the literature (46, 47). Delayed onset of illness in women, and the putative involvement of estrogen in the course of illness and response to treatment in women underscore the importance of gender differences in the course of schizophrenia (48). There are also significant gender differences in bone mineral accrual and loss. Bone is added to the outer cortical shell in boys compared to the inner aspect of the cortex in girls (49). The current study on the potential impact of conventional antipsychotic drugs or risperidone on BMD adds to the gender differences observed in patients with schizophrenia.

Duration of Antipsychotic Treatment and Low BMD

The duration of antipsychotic drug treatment was not significantly correlated with change in T-scores for either gender. This is similar to our earlier findings: the duration of treatment had no significant correlation with the development of hyperprolactinemia (14). There are varying results in the literature concerning duration of antipsychotic drug treatment and treatment-emergent osteoporosis and osteopenia, with some results indicating a positive association (50) while others show no association (26). It is suggested that the risk of developing low BMD may be related to the dopamine blocking properties of antipsychotic drugs rather than the classification as typical or atypical drugs (45).

Limitations

This study was a cross-sectional examination of prolactin level and its potential association with bone loss in patients with schizophrenia treated with conventional antipsychotics or the atypical antipsychotic risperidone. There were no other atypical antipsychotics available at the time of study design (1998) with a similar prolactin profile as the above drugs. This study lacked a control group to compare bone loss in a group of patients treated with antipsychotic drugs having a lower risk of elevated prolactin. The study design also had no controls for some known risk factors for bone loss, such as vitamin D deficiency, lithium, smoking, and alcohol (51). A longitudinal study to assess the time course of hyperprolactinemia on bone loss in both genders would be desirable. A higher percentage of male patients compared to female patients in this study may be considered as a limitation. However, it is not unusual to have male patients more highly represented than female patients in schizophrenia trials and in this trial, 36.6% of the overall sample were female patients, which is consistent with other schizophrenia trials. In this study, lower doses of antipsychotic drugs in women compared to men may be considered as a limitation. However, studies have shown that pharmacokinetics and pharmacodynamics of drugs differ in women compared to men. Therefore, in general, women may require lower doses of medication than men in the treatment of schizophrenia (52, 53). Another potential limitation is that applying the WHO criteria for diagnosing osteoporosis to some types of heel QUS device may underdiagnose the condition (54).

Conclusions

In this large, cross-sectional study represented by both gender patients with schizophrenia, gender differences were observed in the prevalence of low BMD in patients treated with conventional antipsychotics or the atypical antipsychotic risperidone. Contrary to the general trend in which women are at a higher risk of osteopenia compared to men, hyperprolactinemia during treatment with antipsychotic drugs may be associated with a greater prevalence of low bone mass in men compared to women. Elevated prolactin may have a direct effect on the bone, increasing bone turnover in patients of both genders, while hypogonadism may be associated with elevated prolactin in male patients only. Hyperprolactinemia in men may result in low bone density due to an increase in bone resorption rate mediated by decreased testosterone levels. The negative association found between N-telopeptide and testosterone in men suggests that low testosterone is accompanied by high telopeptide, a marker for increased bone resorption. Hyperprolactinemia in women may result in increased bone turnover, yet a decreased prevalence of low BMD compared to men. This may be due to hypogonadism associated with elevated prolactin not applicable in women. Controlling for age, there was no significant correlation between change in T-score and duration of antipsychotic treatment for either gender. Findings from this study underscore the need to evaluate bone health in both men and women treated with antipsychotic drugs that have the propensity to raise prolactin levels.

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