# Prevalence of Bone Mineral Density Loss in Korean Patients With Schizophrenia: A Cross-Sectional Study

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***Objective:*** This study investigates bone mineral density (BMD) and the association between BMD and hormonal changes in Korean patients with schizophrenia.

***Method:*** This cross-sectional study was conducted from January 2005 to June 2005; 195 inpatients with schizophrenia (DSM-IV) were screened. Among them, 51 patients aged 18 to 45 years who had taken haloperidol monotherapy for at least 2 years participated in this study. The control group consisted of normal healthy volunteers who were of similar ages (N = 57). Bone mineral density was determined by a GE Lunar 4500 scanner. Hormone levels were measured by using commercial kits. The Student t test, the Pearson $\chi^2$ test, the Wilcoxon rank sum test, and logistic regression analysis were used for data analysis.

***Results:*** Female patients, but not male patients, showed significantly lower BMD than the normal controls as seen in all bone regions studied. Among 18 female patients with BMD loss, 17 patients showed hyperprolactinemia, and 7 showed combined hypoestrogenemia. Prolactin levels were significantly higher in the female patients with BMD loss compared to those with normal bone density; however, other hormone levels were not different between the 2 groups. There was no significant difference in hormonal levels between bone loss and normal bone density groups.

***Conclusions:*** Bone mineral density loss in patients with schizophrenia tended to differ by gender. Decreased BMD compared to normal controls was seen in female patients; however, this was not observed in men.

*(J Clin Psychiatry 2006;67:1391–1396)*

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*This study was supported by a grant from the Korea Health 21 R&D Project, Ministry of Health & Welfare, Republic of Korea (0412-CT02-0704-0006).*

*The authors report no additional financial or other relationships relevant to the subject of this article.*

*The authors appreciate the help of Jung-Goo Lee, M.D., and Deuk Man Cho, M.D., for referring patients to this study.*

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Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. People with schizophrenia represent a high-risk group for developing osteoporosis because of the disease itself, long-term antipsychotic drug treatment, lack of exercise, poor nutrition, and high rates of smoking.[1,2] Hyperprolactinemia, a common side effect of conventional antipsychotic drugs, is known to increase the risk of bone mineral density (BMD) loss, which is mediated by secondary hypogonadism[3] or hyperprolactinemia itself,[4] in patients with schizophrenia who had been receiving long-term antipsychotic drug treatment.

Previous studies have demonstrated that between 32% and 65% of patients treated with antipsychotic drugs suffer from bone mineral loss, leading to osteoporosis.[3,5] It is also known that the prevalence of BMD loss with aging is different among ethnic populations[6]; however, few data are available on this issue in patients with schizophrenia. In our literature review, we were unable to locate any data on BMD loss among Asian patients with schizophrenia.

To evaluate the prevalence of BMD and its association with hormonal changes in Asian patients with schizophrenia and long-term antipsychotic treatment, we screened and investigated a large population of Korean patients with schizophrenia who had been receiving long-term haloperidol monotherapy.

## METHOD

One hundred ninety-five inpatients with a DSM-IV diagnosis of schizophrenia in Dongseo hospital in the Republic of Korea were screened. Among them, 51 patients (21 women and 30 men) who fulfilled inclusion criteria participated in this study. Inclusion criteria included patients aged 18 to 45 years who had been receiving haloperidol monotherapy for at least 2 years. Patients who were alcohol-dependent or substance abusing, had nutritional impairments, were taking any medication, or had a known medical disorder known to be a risk factor for osteoporosis were excluded. The patients who had clinical signs suggesting an endocrinologic disorder that causes abnormal menstruation were also excluded. All patients were clinically stable and cooperated with the inpatient program of Dongseo hospital, which included 1 hour of exercise daily. Fifty-seven normal controls (23 women and 34 men) were recruited from the medical checkup service center of Dongseo hospital. The controls were people who voluntarily visited the center for a routine medical checkup and were confirmed as not having any medical or psychiatric illness, including drug or alcohol dependence or abuse. All subjects were enrolled into the study after giving written consent. This cross-sectional study, conducted from January 2005 to June 2005, was approved by the Institutional Review Board of Inje University.

Bone densitometry testing was performed by dual energy x-ray absorptiometry (GE Lunar 4500 scanner) in the lumber spine (L1–L4) and in the femoral neck, trochanter, and intertrochanteric regions of the proximal right femur. According to the World Health Organization guidelines, a t score ≥ –1.0 represents normal bone mass. Osteopenia was defined as a t score between –1.0 and –2.5, and osteoporosis was defined as a t score ≤ –2.5.[7] For study purposes, we defined BMD loss as either the presence of osteopenia or osteoporosis (t score < –1.0).

Blood was drawn at the 0900 hour for the analysis of 7 hormones: prolactin, estradiol, testosterone, thyroid-stimulating hormone (TSH), thyroxine ($T_4$), follicle-stimulating hormone (FSH), and luteinizing hormone (LH). For women, the menstrual cycle was not considered at the time of hormone level measurement because 17 of 21 patients had amenorrhea or oligomenorrhea for more than 3 menstrual cycles prior to enrollment into this study. Serum samples were measured by using electrochemiluminescent immunoassays, with commercial kits for prolactin (Elecsys 2010, Boehringer Mannheim, Indianapolis, Ind.) (the interassay coefficient of variation = 4.6%, for a concentration of 4.85 ng/mL), testosterone (Elecsys 2010, Roche, Indianapolis, Ind.) (the interassay coefficient of variation = 2.1%, for a concentration of 0.118 ng/mL), FSH (Elecsys 2010, Roche, Indianapolis, Ind.) (the interassay coefficient of variation = 4.9%, for a concentration of 5.24 mIU/mL), LH (Elecsys 2010, Roche, Indianapolis, Ind.) (the interassay coefficient of variation = 2.2%, for a concentration of 3.47 mIU/mL), TSH (Elecsys 2010, Roche, Indianapolis, Ind.) (the interassay coefficient of variation = 4.1%, for a concentration of 0.14 mIU/L), and $T_4$ levels (Elecsys 2010, Roche, Indianapolis, Ind.) (the interassay coefficient of variation = 4.2%, for a concentration of 0.75 μg/dL). Estradiol was measured by using a microparticle enzyme immunoassay kit (AXSYM, Abbott, Abbott Park, Ill.)(the interassay coefficient of variation was 4.2%, for a concentration of 681 pg/mL). Hyperprolactinemia was defined as a prolactin level > 20 ng/mL for men and > 24 ng/mL for women. Hypoestrogenemia was defined as an estradiol level ≤ 35 pg/mL, and partial androgen deficient syndrome was defined as a testosterone level < 3.0 ng/mL. The Student t test, the Pearson $\chi^2$ test, the Wilcoxon rank sum test, and logistic regression analysis were used for data analysis. All tests were 2-tailed, and significance was defined as $\alpha < .05$.

## RESULTS

### Demographic and Clinical Characteristics

The demographic and clinical characteristics for the subjects are presented in Table 1. Age and body mass index (BMI) were not significantly different between patients and normal controls. No female subject was a smoker. Although the number of smokers was no different between male patients and male controls, the mean ± SD amount of cigarettes smoked daily was significantly higher in patients than in normal controls (19.2 ± 5.1 vs. 12.9 ± 7.0; t = 2.75, df = 26, p = .011). There were no significant differences in age, BMI, and medication history between female and male patients (Table 1).

### Endocrine Assessment

Hormonal levels of patients are shown in Table 1. Hyperprolactinemia was evident in 90.5% (19/21) of female patients, while in 40.0% (12/30) of male patients. The mean prolactin levels were significantly higher in female patients than in male patients (t = 5.05, df = 49, p = .0001).

Of the 21 female patients, 17 had abnormal menstruation (oligomenorrhea or amenorrhea), while 4 patients had normal menstruation. All 17 patients with abnormal menstruation showed hyperprolactinemia, while 2 of the 4 patients with normal menstruation showed hyperprolactinemia. Patients with abnormal menstruation showed significantly higher prolactin levels than those with normal menstruation (mean ± SD = 77.8 ± 49.1 ng/mL vs. 33.9 ± 30.2 ng/mL; Wilcoxon = 18, p = .0033). The ranges of prolactin levels were from 27.2 ng/mL to 224.3 ng/mL in patients with abnormal menstruation and from

**Table 1. Demographic and Clinical Characteristics of Patients With Schizophrenia and Normal Controls**

| Characteristic | Patients With Schizophrenia (N = 51) | | Normal Controls (N = 57) | |
|---|---|---|---|---|
| | Women (N = 21) | Men (N = 30) | Women (N = 23) | Men (N = 34) |
| Age, mean ± SD, y | 37.8 ± 5.5 | 39.9 ± 5.1 | 40.3 ± 3.3 | 36.9 ± 6.5 |
| Body mass index, mean ± SD, kg/m$^2$ | 23.5 ± 3.4 | 23.9 ± 5.6 | 22.8 ± 4.9 | 24.1 ± 4.8 |
| Duration of haloperidol treatment, mean ± SD, mo | 84.5 ± 62.2 | 89.5 ± 59.5 | … | … |
| Haloperidol dose, mg/d | | | | |
| Mean ± SD | 14.5 ± 11.8 | 15.3 ± 11.0 | … | … |
| Median ± IQR | 11.0 ± 9.1 | 13.0 ± 11.1 | … | … |
| Smoking history | | | | |
| No. of smokers, N (%) | 0 (0) | 15 (50.0) | 0 (0) | 13 (38.2) |
| Cigarettes smoked per day, mean ± SD | 0 | 19.2 ± 5.1* | 0 | 12.9 ± 7.0* |
| Hormone levels, mean ± SD | | | | |
| Prolactin, ng/mL | 69.5 ± 48.8 | 22.2 ± 13.8** | … | … |
| Estradiol, pg/mL | 52.4 ± 34.6 | 37.2 ± 10.7 | … | … |
| Testosterone, ng/mL | 0.3 ± 0.1 | 9.6 ± 3.5** | … | … |
| FSH, mIU/mL | 8.9 ± 5.0 | 4.7 ± 2.0** | … | … |
| LH, mIU/mL | 6.7 ± 3.7 | 4.2 ± 1.6** | … | … |
| TSH, mIU/L | 1.2 ± 0.2 | 2.0 ± 1.1 | … | … |
| $T_4$, μg/dL | 2.5 ± 2.3 | 1.4 ± 0.2 | … | … |

*p < .05; male patients compared to male controls.
**p < .01; male patients compared to female patients.
Abbreviations: FSH = follicle-stimulating hormone, IQR = interquartile range, LH = luteinizing hormone, $T_4$ = thyroxine, TSH = thyroid-stimulating hormone.

9.3 ng/mL to 77.8 ng/mL for those with normal menstruation. The estradiol levels of patients with abnormal menstruation were not significantly different compared to those of patients with normal menstruation (mean ± SD = 52.0 ± 37.4 pg/mL vs. 53.7 ± 21.5 pg/mL). The range of estradiol in women with abnormal menstruation was between 19.63 pg/mL and 126.36 pg/mL. Seven female patients with abnormal menstruation showed both hyperprolactinemia and hypoestrogenemia simultaneously, and the other 10 patients showed only hyperprolactinemia without hypoestrogenemia. Follicle-stimulating hormone (mean ± SD = 8.9 ± 5.0 mIU/mL; range, 2.0 mIU/mL to 22.8 mIU/mL) and LH (mean ± SD = 6.7 ± 3.7 mIU/mL; range, 2.0 mIU/mL to 15.1 mIU/mL) levels in female patients were within the normal range. These results demonstrate that abnormal menstruation in our patients was not due to menopause. The mean ± SD levels of testosterone, $T_4$, and TSH in female patients were 0.3 ± 0.1 ng/mL, 2.5 ± 2.3 μg/dL, and 1.2 ± 0.2 mIU/L, respectively. No significant correlation was found among the levels of prolactin, estradiol, FSH, testosterone, LH, $T_4$, and TSH.

In the 30 male patients, 12 (40.0%) had hyperprolactinemia with a mean ± SD prolactin level of 22.2 ± 13.8 ng/mL (range, 5.1 ng/mL to 70.3 ng/mL). Six male patients (4 patients with bone loss, 2 patients with normal bone density) showed partial androgen deficiency, and 3 of them had combined hyperprolactinemia. The mean ± SD testosterone level was 9.6 ± 3.5 ng/mL (range, 2.3 ng/mL to 8.8 ng/mL). The mean ± SD levels of estradiol, FSH, LH, TSH, and $T_4$ were 37.2 ± 10.7 pg/mL, 4.7 ± 2.0 mIU/mL, 4.2 ± 1.6 mIU/mL, 2.0 ± 1.1 mIU/L, and 1.4 ± 0.2 μg/dL, respectively.

### Bone Mineral Density Assessment

A significantly higher percentage of patients with schizophrenia (64.7%, 33/51) had decreased bone loss as compared to the normal controls (43.9%, 25/57) ($\chi^2 = 4.70$, df = 1, p = .003). In the schizophrenia group, those with BMD loss were composed of 52.9% (27/51) with osteopenia and 11.8% (6/51) with osteoporosis. As for the normal controls with BMD loss, 36.8% (21/57) had osteopenia and 7.0% (4/57) had osteoporosis. In the schizophrenia group, age, BMI, duration of haloperidol use, and dose of haloperidol were not significantly correlated with the BMD loss. However, gender played a significant role in the findings; a significantly higher percentage of female patients (85.7%, 18/21) showed decreased BMD as compared to male patients (50.0%, 15/30) ($\chi^2 = 6.899$, df = 1, p = .008). In normal controls, BMD loss was not correlated with age, BMI, or gender (39.1% [9/23] of women vs. 47.1% [16/34] of men).

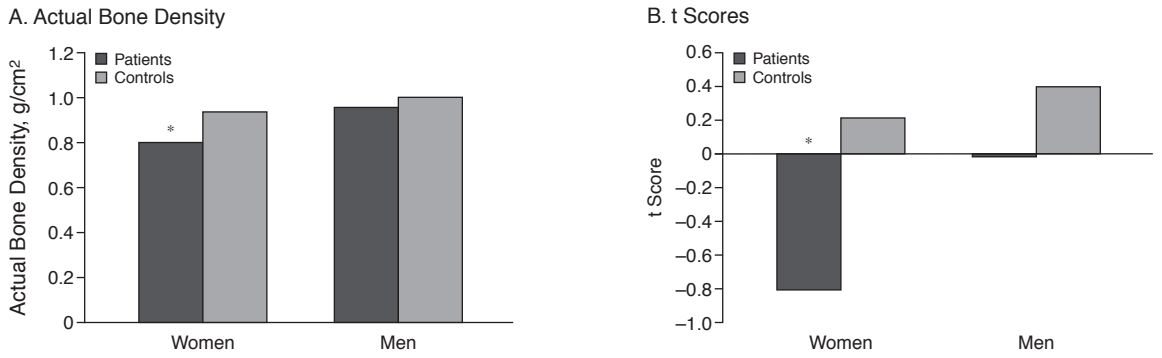
The actual bone density and t scores in the lumbar and 3 femur sites were significantly lower in the patients as compared to the normal controls. However, when genders were analyzed separately, only the female patients had significantly lower both absolute bone density and t scores than normal women, and this was evident in all bone regions studied; no differences in men were noted (Table 2, Figure 1).

Table 2. Comparison of Absolute Value and t Scores of Bone Mass Density on the Lumbar (L1–L4) and Femur Sites Between Patients With Schizophrenia (N = 51) and Normal Controls (N = 57)[a]

| | Total | | Women | | Men | |
|---|---|---|---|---|---|---|
| Measurement | Patients | Controls | Patients | Controls | Patients | Controls |
| Actual bone density, mean ± SD, g/cm$^2$ | | | | | | |
| L1–L4 | 1.13 ± 0.13* | 1.20 ± 0.13 | 1.09 ± 0.13** | 1.20 ± 0.12 | 1.16 ± 0.13 | 1.20 ± 0.13 |
| Femur | | | | | | |
| Neck | 0.89 ± 0.14** | 0.97 ± 0.13 | 0.80 ± 0.11** | 0.93 ± 0.14 | 0.95 ± 0.14 | 1.00 ± 0.11 |
| Ward | 0.78 ± 0.14** | 0.87 ± 0.15 | 0.71 ± 0.13** | 0.87 ± 0.18 | 0.84 ± 0.13 | 0.87 ± 0.12 |
| Trochanter | 0.77 ± 0.14** | 0.85 ± 0.13 | 0.68 ± 0.09** | 0.80 ± 0.12 | 0.83 ± 0.12 | 0.88 ± 0.13 |
| t Score, mean ± SD | | | | | | |
| L1–L4 | –0.14 ± 1.06* | 0.39 ± 1.11 | –0.13 ± 1.08** | 0.74 ± 1.01 | –0.15 ± 1.07 | 0.16 ± 1.13 |
| Femur | | | | | | |
| Neck | –0.35 ± 1.07** | 0.32 ± 0.99 | –0.81 ± 0.91** | 0.21 ± 1.15 | –0.02 ± 1.06 | 0.40 ± 0.87 |
| Ward | –0.73 ± 1.11** | –0.13 ± 1.13 | –1.29 ± 1.01** | –0.17 ± 1.38 | –0.34 ± 1.02 | –0.11 ± 0.95 |
| Trochanter | 0.00 ± 1.16** | 0.73 ± 1.19 | –0.67 ± 0.84** | 0.46 ± 1.12 | 0.46 ± 1.14 | 0.91 ± 1.22 |

[a]Scores of patients and normal controls were compared by total (women + men), women, and men separately.
*p < .05; patients vs. controls.
**p < .005; patients vs. controls.

Figure 1. Actual Bone Density and t Scores of Femur Neck, by Sex and Group




*p < .005 (patients vs. controls).

### Hormone Level and Bone Mineral Density

Among the 18 female patients with BMD loss, 7 patients (38.9%) had hyperprolactinemia combined with hypoestrogenemia, 10 patients (55.6%) had only hyperprolactinemia without hypoestrogenemia, and 1 patient (5.6%) had a normal range of prolactin and estradiol levels. No significant differences were found in actual bone density and t scores at all sites in female patients who had hyperprolactinemia with and without hypoestrogenemia. Prolactin levels were significantly higher in the female patients with BMD loss as compared to those with normal bone density (mean ± SD = 72.5 ± 49.7 ng/mL vs. mean ± SD = 42.1 ± 31.2 ng/mL) (Wilcoxon = 32.5, p = .043). The estradiol, testosterone, free testosterone, LH, and FSH levels were not different between the 2 groups and were not correlated with bone loss.

Male patients with BMD loss showed no significant differences in the levels of prolactin, testosterone, and free testosterone compared to those of patients with normal bone density. Prolactin, testosterone, free testosterone, estradiol, LH, and FSH levels were not correlated with actual bone density and t scores at any of the sites.

## DISCUSSION

This study demonstrates that female, but not male, patients with schizophrenia having long-term exposure to haloperidol showed significantly decreased BMD as compared with similarly aged normal controls. In our study, the prevalence of bone loss in schizophrenia was higher than that in previous studies that were done in white, African, and Caribbean populations,[5] possibly reflecting an interethnic difference in BMD loss.

It has been established that patients with schizophrenia are at risk for BMD loss.[8] Our results also show that patients with schizophrenia have a decreased BMD compared with normal controls; however, this is only significant for the female patients. Aging in women is known to be a risk factor for BMD loss,[9] and this gender specificity on BMD loss tends to be more apparent after meno-

pause.[10] In the present study, however, we were unable to detect an effect of BMD loss with aging. This may be due to the fact that most patients were around 40 years old, with little range of age noted. Also, contrary to our findings, some previous studies[11,12] have reported that male patients with schizophrenia are more severely affected than women with schizophrenia regarding bone loss. Previous authors have theorized that the early onset of illness in men and the tendency to take less care of themselves may relate to the previous findings of lower bone mass in males. Although our finding indicating that a higher prevalence of BMD loss is present in women as compared to men is not easily explained, we believe that hormonal changes induced by antipsychotic drugs may be more common and may contribute to an increased bone loss in women than men. Additionally, our study actually compared the prevalence of bone loss in patients with schizophrenia to normal controls, while previous studies have only relied upon reference data from the normal population. According to our literature review, this is the first report comparing BMD in schizophrenia patients to normal controls.

In our study, 85.7% of women and 50.0% of men showed BMD loss. Even considering sex differences, the prevalence of bone loss in our study was higher than that in the previous studies. Meaney et al.[3] reported age-related BMD loss in 57% of men and 32% of women with schizophrenia. O'Keane and Meaney[5] demonstrated that 65% of young women with schizophrenia treated with prolactin-raising antipsychotic drugs showed low BMD. This may be due to the differences in study design. First, the previous studies included patients treated with various kinds of antipsychotic drugs, while our study included those treated with haloperidol monotherapy. Recent reports suggest that some atypical antipsychotic drugs may be less harmful to bone than conventional drugs.[13] The differences in duration of psychotic illness and antipsychotic drug treatment between those studies and our study may also contribute to different results as seen previously. Furthermore, the subjects of previous studies were outpatients, while all subjects in our study were inpatients. Interethnic difference in bone density should also be considered. Other studies have reported that African Americans have higher bone mass and a substantially lower fracture rate than age-matched white subjects.[14,15] Asians have been found to have the lowest bone density, as compared with other populations such as the African American, Hispanic, Native American, and white populations.[15] For reasons still not known, a variety of genetic and environmental factors such as diet may be related to the ethnic differences in peak bone mass and the development of osteoporosis.[16] However, our finding of BMD loss should be interpreted carefully, because many compounding factors such as differences in the measuring site used, the age range of study participants, and the reference population can influence this different rate of bone loss between our study and previous studies.

In terms of the effects of antipsychotic drugs on BMD, longer duration and higher dose of antipsychotic drug treatment have been considered as high risk factors for bone loss.[3,13,17] However, we did not find a significant correlation between bone loss and the duration and mean dose of haloperidol treatment. The similar characteristics regarding medication history in our subjects may contribute to this finding.

In the present study, 94.4% (17/18) of the female patients with BMD loss had hyperprolactinemia, and prolactin levels were significantly higher in patients with bone loss than those with normal bone density. However, generally it has been known that the extent of bone loss correlates with the duration rather than the degree of hyperprolactinemia.[18] The most common explanation about bone loss associated with antipsychotic treatment has been focused on secondary hypogonadism, which is mediated by hyperprolactinemic states as a side effect of antipsychotic drug treatment. In a study focusing on risk factors for osteoporosis in young females with schizophrenia, O'Keane and Meaney[5] reported that prolactin levels were predictive of reduced lumbar BMD values and that high prolactin levels were significantly associated with low sex hormone levels. On the other hand, Abraham et al.[4] reported that patients with bone loss and hyperprolactinemia did not have hypogonadism. In our study, among 18 female patients with BMD loss, 7 patients (38.9%) had hyperprolactinemia combined with hypoestrogenemia, and 10 patients (55.6%) had only hyperprolactinemia without hypoestrogenemia. Among the 17 patients with hyperprolactinemia, 7 patients (41.2%) had hyperprolactinemia with hypoestrogenemia, and 9 patients (52.9%) had only hyperprolactinemia without hypoestrogenemia. Additionally, we found no significant differences in actual bone density and t scores at all sites between patients with hyperprolactinemia and hypoestrogenemia and those with only hyperprolactinemia.

Sustained amenorrhea is known to be a high risk factor for bone loss.[18] In our study, 17 female patients (15 patients with bone loss and 2 patients with normal bone density) experienced abnormal menstruation. Among them, 7 (46.7%) of the 15 patients with bone loss had hyperprolactinemia with hypoestrogenemia and 8 (53.3%) of the 15 had only hyperprolactinemia without hypoestrogenemia. Nevertheless, our data may not be sufficient to explain the effect of prolactin and estradiol on bone loss in patients with schizophrenia. One should interpret our findings with caution, because these findings were acquired from a 1-point study on hormone and menstrual disturbance by cross-sectional design, with a too small sample size of normal menstruation patients. Also, estradiol levels were not timed to the menstrual cycle. In addition, there may be factors other than hyperprolactinemia and/or hypoestro-

genemia that cause bone loss. Finally, the definition of hypoestrogenemia can be argued because in the presence of normal menstruation, and even in patients with oligomenorrhea, a low estradiol level cannot be interpreted as hypoestrogenemia.

Previous studies reported that the primary mechanism of bone loss in males, like females, is the result of hypogonadism, which occurs in males with hyperprolactinemia.[18,19] In our study, male patients with BMD loss showed no significant difference in prolactin and testosterone levels compared to those of patients with normal bone density. Moreover, the prevalence of hyperprolactinemia and partial androgen deficiency was not significantly different between the 2 groups. Although we could not explain the reason of this discrepancy with our findings, several confounding factors such as age and other factors beside sex hormonal changes might contribute to this difference.

Several limitations should be considered in interpreting the findings of this report. First, BMD loss in the patients with schizophrenia is influenced by several factors. We have evaluated the effect of antipsychotic drugs without the exclusion of other potential variables such as smoking, nutrition, activity level, family history of bone loss, and the deficiency of calcium and vitamin D. Long-term, prospective studies are needed to exclude the effects of those factors. Second, our study did not have a comparison group of drug naive patients with schizophrenia; however, the comparison of BMD loss in patients with the normal controls may be helpful to understand the risk of bone loss in patients with schizophrenia who inevitably are treated with antipsychotic agents. Finally, because we did not evaluate endocrinologic assessment in normal controls, the hormonal changes and BMD loss in patients were not compared to those in controls.

Our results emphasize that the effect of antipsychotic drugs, particularly haloperidol, on BMD loss is more powerful in women than men and that the risk of BMD loss by antipsychotic drug may be varied by ethnicity. Although hyperprolactinemia may be associated with bone loss in patients with schizophrenia, it needs to be confirmed by further study.

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