Antipsychotic-Induced Hyperprolactinemia Inhibits the Hypothalamo-Pituitary-Gonadal Axis and Reduces Bone Mineral Density in Male Patients With Schizophrenia

Taishiro Kishimoto, M.D.; Koichiro Watanabe, M.D., Ph.D.; Naoki Shimada, M.D., Ph.D.; Kazuya Makita, M.D., Ph.D.; Gohei Yagi, M.D., Ph.D.; and Haruo Kashima, M.D., Ph.D.

Objective: An inhibitory effect of hyperprolactinemia on the hypothalamo-pituitary-gonadal axis has been suggested as a mechanism of bone loss in schizophrenia, but this has not been confirmed. In this study, which was conducted in Tokyo, Japan, from February to May 2005, we examined the possible causes of reduced bone mineral density (BMD) in male patients with schizophrenia.

Method: The BMD of the radius of 74 male patients (aged 31–78 years) who met the diagnostic criteria for DSM-IV schizophrenia was measured by dual-energy x-ray absorptiometry. Levels of prolactin (PRL), follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone, estradiol, and 1,25-dihydroxy vitamin D (VitD) were also measured. Pedometers were used to measure the impact of exercise.

Results: Study subjects showed lower BMD in all age groups compared with reference values in healthy persons. There was no significant difference in the Z score among low, medium, and high exercise groups. 87% of the subjects had hyperprolactinemia, and VitD levels were normal in all subjects except 1. The high PRL group had lower levels of FSH and LH, and significantly lower levels of estradiol ($p < .05$), compared with the normal PRL group. In the high PRL group, there was a significant negative correlation between the duration of treatment and the Z score ($p < .05$).

Conclusion: Male patients with schizophrenia had lower BMD than normal individuals irrespective of the amount of exercise or the level of VitD. The results support the hypothesis that inhibition of the hypothalamo-pituitary-gonadal axis by hyperprolactinemia contributes to the mechanism of the bone loss and suggest that the longer the duration of hyperprolactinemia, the greater the reduction in BMD.

(J Clin Psychiatry 2008;69:385–391)

Received Aug. 11, 2006; accepted Aug. 6, 2007. From Oizumi Hospital (Dr. Kishimoto); the Department of Neuropsychiatry (Drs. Kishimoto, Watanabe, and Kashima), the Department of Preventive Medicine and Public Health (Dr. Shimada), and the Department of Obstetrics and Gynecology (Dr. Makita), Keio University School of Medicine, Tokyo; and Suisei Healing Center, Kanagawa (Dr. Yagi), Japan.

This study was partly supported by Dainippon Sumitomo Pharma, Osaka, Japan.

The results of this study were presented at the 25th Collegium Internationale Neuro-Psychopharmacologicum Congress, July 9–13, 2006, Chicago, Ill.

The authors thank Koichi Ishii, M.D.; Shingo Katayama, M.D., Ph.D.; and Yasushi Imasaka, M.D., Ph.D., for their help and advice. The acknowledged individuals report no financial affiliations or other relationships relevant to the subject of this article.

Dr. Watanabe has received grant/research support from Dainippon Sumitomo Pharma, Eli Lilly, GlaxoSmithKline, Janssen, and Pfizer; and has received honoraria from Dainippon Sumitomo Pharma, Eli Lilly, GlaxoSmithKline, Janssen, Otsuka, and Pfizer. Drs. Kishimoto, Shimada, Makita, Yagi, and Kashima report no financial affiliations or other relationships relevant to the subject of this article.

Corresponding author and reprints: Taishiro Kishimoto, M.D., Oizumi Hospital, 6-9-1 Oizumigakuen-cho Nerima-ku Tokyo 178-0061, Japan (e-mail: taishiro-k@mti.biglobe.ne.jp).

While lower bone mineral density (BMD) among schizophrenia patients was noted a relatively long time ago,[1,2] insufficient attention has been paid to the phenomenon, and the causes of low BMD and the countermeasures that can be taken have not been sufficiently investigated. Recently, the relationship between schizophrenia and lower BMD has attracted attention,[3–5] and its causes have been discussed.

It is suspected that antipsychotic medication has an inhibitory effect on the hypothalamo-pituitary-gonadal axis and that this is a part of the mechanism by which BMD is lowered in patients with schizophrenia.[6] It is believed that the secretion of gonadotropin-releasing hormone (GnRH) in the hypothalamus is suppressed when the level of prolactin (PRL) rises after administration of the antipsychotics, which then causes lowered secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in the pituitary and consequent lowered secretion of sex hormones such as estradiol and testosterone in the gonads, leading to abnormal bone metabolism similar to

that associated with postmenopausal osteoporosis. However, this hypothesis has not been rigorously tested in previous studies, and a number of researchers deny any relationship between bone metabolism and PRL.[7] In particular, many aspects of the mechanism of bone loss in males remain unclear. Insufficient exercise, smoking, and calcium and vitamin D deficiencies are among the risk factors for osteopenia. Because these factors are often present in patients with schizophrenia, it has been difficult to elucidate the relationship between PRL and bone metabolism.

We studied bone metabolism in male patients with schizophrenia, and discuss the mechanism of bone loss in these patients taking into account the effects of the amount of exercise and exposure to sunlight. Our present study is the largest among similar studies conducted so far.

METHOD

Subjects

This study was conducted with the approval of the Ethics Committee of the Oizumi Hospital. Out of 92 male patients aged ≥ 30 years who were hospitalized at the Oizumi Hospital in Tokyo, Japan, from February to May 2005 and met the diagnostic criteria for DSM-IV schizophrenia, 74 (aged 31–78 years) gave written consent after understanding the aims of the study and were included. Those patients with psychiatric comorbidities that might affect BMD, such as an eating disorder, substance abuse, and alcohol dependence, were excluded from the study population. Regular evaluation confirmed that patients showed no abnormalities in biochemical parameters such as calcium and phosphate levels. Other exclusion criteria included disease complications that might disturb bone metabolism, such as bone metabolism disorders, thyroid dysfunction (abnormalities in thyroid-stimulating hormone and free T_3 and T_4 levels were ruled out), and hyperparathyroidism; medication with steroids or thyroxines; and pharmacotherapy for osteoporosis. During hospitalization, subjects received well-balanced meals containing the recommended amount of calcium for Japanese men (600 mg/day).

Measures

The BMD of the radius of the subjects was measured by dual-energy x-ray absorptiometry (DEXA) (Aloka Dicroma scan DCS-600EX-3, Aloka Co., Ltd., Tokyo, Japan). The BMD was measured at the distal one-third portion of the radius of the arm contralateral to the dominant arm of the subject and expressed as the measured value, T score, and Z score for comparison. The T score and Z score were defined as follows:

T = (BMD of the subject – YAM) / YASD
Z = (BMD of the subject – mean BMD of the age-matched group) / standard deviation of the BMD of the age-matched group

The YAM (young adult mean) is the mean BMD for young adults and the YASD (young adult standard deviation) is the standard deviation of the mean BMD of young adults. A T score compares the subject's bone density to the optimal peak bone density for gender. A T score of –1 to –2.5 is considered osteopenic and a risk for developing osteoporosis. A T score of ≤ –2.5 is diagnostic of osteoporosis.[8] In contrast, a Z score compares the subject's bone density to the mean bone density of healthy persons of the same age and gender. In this study, a Z score was used to make a comparison among subjects in order to minimize the effect of age, as there was wide variation in the subjects' ages in the study.

The subjects' blood was sampled between 6 a.m. and 8 a.m., and the PRL, FSH, LH, testosterone, estradiol, and 1,25-dihydroxy vitamin D (VitD) levels were measured. The following measurement methods were used: for PRL, LH, and FSH, a chemiluminescence immunoassay kit from ARCHITECT (Abbott Japan, Roppongi, Minato-ku, Tokyo); for testosterone, the ECLusys system from Roche Diagnostic (Basel, Switzerland) (based on an electrochemiluminescence immunoassay method); for estradiol, the AxSYM system from Abbott Japan (Roppongi, Minato-ku, Tokyo) (based on Microparticle Enzyme Immunoassay technology); and for VitD, a TFB radioimmunoassay kit from Immunodiagnostic Systems, Inc. (Scottsdale, Ariz.).

Among the 74 subjects in this study, 48 were receiving antipsychotic combination therapy and 26 were receiving antipsychotic monotherapy (among those 26, nineteen were receiving atypical antipsychotic monotherapy). Therefore, it was difficult to analyze PRL and BMD for each antipsychotic agent. To resolve this difficulty, antipsychotics were classified into PRL-raising or PRL-sparing antipsychotics, and the subjects were divided into 2 groups, 1 group receiving ≥ 1 PRL-raising antipsychotics and a group not receiving PRL-raising antipsychotics.

Prolactin-sparing antipsychotics include olanzapine, quetiapine, aripiprazole, and perospirone (a serotonin-dopamine antagonist; available only in Japan), and PRL-raising antipsychotics include first-generation antipsychotics and risperidone.[9–11] Furthermore, the subjects were grouped into 2 groups according to their PRL levels, a normal PRL group (PRL ≤ 12.78 ng/mL) and a high PRL group (PRL > 12.78 ng/mL), in order to analyze PRL effects on other hormones and BMD. The normal range of PRL levels was determined after log transforming the PRL levels of 59 healthy Japanese male subjects measured by the same method as used in this study and taking the mean value ± 2SD.[12]

The details of the subjects' prescriptions, other diseases present, and the history of treatment were obtained from case records. The smoking and drinking habits of the subjects were recorded through semistructured clinical

interviews. Mental symptoms were evaluated using the Brief Psychiatric Rating Scale (BPRS),[13] and the amounts of antipsychotics administered were expressed as chlorpromazine equivalents.[14] The amount of exercise undertaken by each subject was measured with a pedometer (Tanita FB-714 with "fat burned" counter, Tanita Corporation, Maenocho Itabashi-ku, Tokyo, Japan.). The pedometer was worn on the subject's waist and added 1 count each time the subject took a step. Before taking the measurements, the subjects were asked to undertake a trial walk wearing the pedometer to confirm that the pedometer recorded the actual number of steps walked and that it did not record other movements, such as tremors. The subjects wore the pedometers for 48 to 72 hours, and the mean number of steps per 24 hours was calculated. Based on the results, the subjects were classified into low (< 5000 steps/day), medium (5000–9999 steps/day), and high (≥ 10,000 steps/day) exercise groups. Each subject's body mass index was calculated from their body weight and height measured within 1 month of the BMD measurements.

Statistical Analysis

The T scores and Z scores were calculated by the method mentioned previously from the BMD data. The measured BMD values of the patients with schizophrenia were stratified into 5-year age intervals and compared with reference data instead of recruiting a control group. The reference data were obtained using the same measurement tools from 3100 healthy males matched for age and race. Because there was wide variation in the subjects' ages in this study, to adjust for the effect of age, the Z scores were used for comparing the BMD between smokers and nonsmokers; among low, medium, and high exercise groups; and between normal and high PRL groups and were also used for testing correlations.

SPSS 15.0J for Windows (SPSS Inc., Chicago, Ill.) was used for the statistical analyses. The differences between the means of 2 groups were tested by the Student t test or the Welch test. Relationships between pairs of variables were examined using Pearson product-moment correlation coefficients.

RESULTS

Table 1 shows the demographic characteristics of the study population. Osteopenia (T score of –1 to –2.5) was observed in 37.8% (28/74) of the subjects, and 27.0% (20/74) had osteoporosis (T score ≤ –2.5).

Figure 1 shows the comparison of BMD between the patients with schizophrenia and healthy Japanese males by age group. The bone density in patients with schizophrenia was lower than the reference values of healthy persons in all age groups, with significant differences ($p < .05$) in all but 3 of the 10 age groups (30–34, 35–39, and 50–54 years).

Table 1. Baseline Demographic Characteristics of Participants With Schizophrenia (N = 74)

Characteristic	Mean	SD
Age, y	58.9	12.2
Duration of illness, y	34.6	13.0
Treatment duration, y	29.6	14.8
Brief Psychiatric Rating Scale score	38.8	11.0
Treatment dose[a]	751.3	590.0
Smokers (N = 37), no. of cigarettes smoked/d	19.2	10.6
Combination therapy, dose, mg/d		
Lithium carbonate (N = 4)	700	115
Sodium valproate (N = 5)	800	283
Carbamazepine (N = 3)	733	155

[a]Dose in mg chlorpromazine equivalents per day.

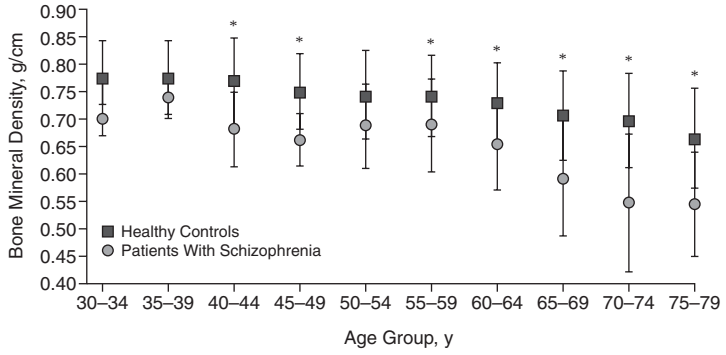
No statistically significant differences in the Z scores were found among patients receiving combination therapy with sodium valproate, patients receiving combination therapy with carbamazepine, and subjects with no combination therapy with anticonvulsants (combination therapy with sodium valproate: N = 5, mean ± SD Z score = –0.59 ± 1.69; combination therapy with carbamazepine: N = 3, mean ± SD Z score = –1.01 ± 1.02; no combination therapy with epileptics: N = 68, mean ± SD Z score = –1.24 ± 1.24).

Among the 74 participants who volunteered for blood sampling, BMD measurement, and other tests, 11 stopped wearing the pedometer for reasons such as "wearing a pedometer for a long time was bothersome or uncomfortable." The remaining 63 participants completed the pedometer test, and among them 27 were in the low exercise group (< 5000 steps/day), 20 were in the medium exercise group (5000–9999 steps/day) and 16 were in the high exercise group (≥ 10,000 steps/day). The respective mean ± SD Z scores for the low, medium, and high exercise groups were –1.45 ± 1.35, –0.84 ± 1.30, and –1.05 ± 1.22, with no significant differences among the groups. There was also no significant difference between the mean ± SD Z scores of smokers (–1.19 ± 1.31) and nonsmokers (–1.18 ± 1.23). All except one subject had normal VitD levels.

Among the 74 subjects, 57 used at least one PRL-raising antipsychotic, and 17 used no PRL-raising antipsychotics. The difference in the mean ± SD PRL levels for each group was statistically significant (31.3 ± 13.8 ng/mL vs. 15.9 ± 11.2 ng/mL, respectively, $p < .001$), and the percentages of subjects with hyperprolactinemia were 94.7% (54/57) in the group using ≥ 1 PRL-raising antipsychotic and 58.8% (10/17) in the group using no PRL-raising antipsychotics. No statistically significant differences were found in gonadotropin, sex hormones, or Z scores for BMD between these 2 groups.

A total of 87% (64/74) of subjects were hyperprolactinemic. Table 2 compares the high and normal PRL groups. The high PRL group generally had low Z scores, although the difference compared with the normal PRL group was not statistically significant. Endocrinologic tests showed

Figure 1. Comparison of Bone Mineral Density Between Patients With Schizophrenia (N = 74) and Healthy Controls (reference data) by Age Group[a]



[a]Data are presented as mean ± SD.
*p < .05.

Table 2. Z Scores and Hormone Levels in Normal Versus High Prolactin (PRL) Groups

	Normal PRL Group[a] (N = 10)		High PRL Group[b] (N = 64)	
Variable	Mean	SD	Mean	SD
PRL, ng/mL**	8.71	2.89	30.70	13.47
FSH, mIU/mL	19.08	18.82	10.37	12.05
LH, mIU/mL	12.87	11.89	7.58	6.91
Testosterone, ng/mL	5.82	1.65	5.49	1.84
Estradiol, pg/mL*	40.00	9.49	32.63	10.06
Z score	–0.95	1.40	–1.22	1.24

[a]Normal PRL group: PRL ≤ 12.78 ng/mL.
[b]High PRL group: PRL > 12.78 ng/mL.
*p < .05.
**p < .01.
Abbreviations: FSH = follicle-stimulating hormone, LH = luteinizing hormone.

that the high PRL group had generally lower FSH and LH levels and significantly lower estradiol levels ($p < .05$).

Correlations with all factors that could affect BMD were tested. Body mass index, chlorpromazine equivalent treatment doses, BPRS scores, PRL levels, and sex hormones were found to have no significant correlation with Z scores.

Similar tests were carried out separately for subjects with normal and high PRL levels. There was negative correlation between the duration of illness and the Z score in both the normal and high PRL groups ($r = –0.69$, $p < .05$; $r = –0.27$, $p < .05$, respectively). Among the subjects with high PRL levels, there was a significant negative correlation between the duration of treatment and Z score ($r = –0.27$, $p < .05$; Figure 2), whereas there was no correlation between the duration of treatment and Z score in the normal PRL group.

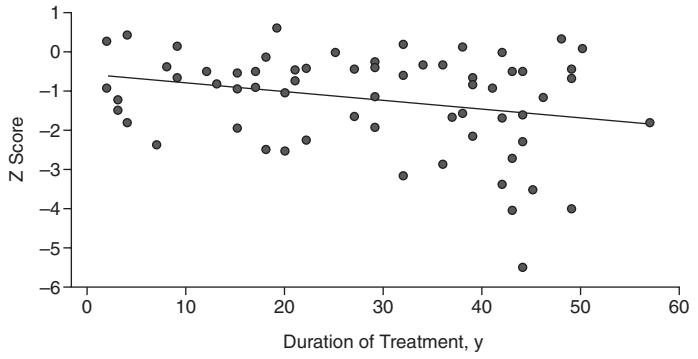
DISCUSSION

To the best of our knowledge, the present study is the largest so far on BMD in male patients with schizophrenia, and it has yielded 3 significant findings. The first finding was the confirmation of the high incidence of osteoporosis among male patients with schizophrenia hospitalized for long periods compared with healthy individuals. The second finding was that, compared with the normal PRL group, the high PRL group tended to have lower FSH and LH levels and had significantly lower estradiol levels. These results support the hypothesis of high PRL levels inhibiting the hypothalamo-pituitary-gonadal axis, which has not been confirmed so far. This finding has significant implications, as it suggests a contributory role for antipsychotic medications in the mechanisms associated with BMD reductions in patients with schizophrenia. The third finding was that longer treatment periods were associated with lower BMD in the high PRL group, even though there was no correlation between the PRL levels themselves and the Z scores. This suggests that the duration of elevated PRL levels may have a more potent effect on BMD reduction than the severity of hyperprolactinemia.

Regarding the incidence of osteoporosis among patients with schizophrenia, the study population might be considered as being nonrepresentative of all patients with schizophrenia, as the study was conducted on hospitalized patients, many of whom had been in hospital for long periods of time. Nevertheless, especially in Japan, many patients with schizophrenia are hospitalized for long periods for social reasons, and it is expected that a large proportion of such populations would have osteopenia or osteoporosis. Osteoporosis can cause spinal fractures and other complications,[15] and not only lowers Activities of Daily Life scores but is also associated with increased mortality.[16] Educating the public about the issues surrounding low BMD and osteoporosis among patients with schizophrenia, early detection of osteoporosis, and establishing effective therapies for schizophrenia are desirable strategies for the future.

Regarding the mechanism of BMD reduction in patients with schizophrenia, which is related to the second finding in the present study, O'Keane and Meaney[17] have reported that in their studies on female patients with schizophrenia, those who had received prolactin-raising antipsychotic medication had lowered estradiol levels and higher incidences of osteoporosis and osteopenia. Becker et al.[18] compared risperidone-treated patients with olanzapine-treated patients and found that the BMD was generally lower in the patients receiving risperidone, a prolactin-raising antipsychotic. Abraham et al.,[19] who followed patients with schizophrenia and high or low PRL levels for 1 year, reported that bone formation and resorption markers increased in the high PRL group and sug-

Figure 2. Correlation Between Z Scores and Treatment Duration in Patients in the High Prolactin Group ($r = -0.27$; $p < .05$)



gested that high PRL levels may have an adverse impact on bone metabolism over time. On the other hand, Meaney et al.[4] reported that the dose of antipsychotic drugs was correlated with Z score but PRL level was not. In a comparative study of patients with schizophrenia, Hummer et al.[7] reported that the 57 male patients included had significantly lower BMD than healthy males, but that BMD was not related to PRL levels. Thus, there is presently no agreement among researchers on the effect of PRL on BMD.

It is known that, as is also the case in the hypothalamo-pituitary-ovarian axis in females, GnRH promotes the release of LH and FSH from the pituitary, which in turn acts on the testes in males, leading to secretion of testosterone. Also, 70% of the estradiol in males is synthesized through aromatization of testosterone and androstenedione in the circulating blood, with the remaining 30% being secreted from the testes.[20] However, not enough information has been gathered on the effects of these sex hormones on bone; i.e., it is not well understood which estrogens or androgens have a strong effect on bone metabolism in males. Finkelstein et al.[21] have reported that BMD in male patients with idiopathic hypogonadotropic hypogonadism was ≤ 2 SD lower than in healthy individuals. On the other hand, a clinical case report[22] of a patient with abnormal estrogen receptors showed several clinical signs of abnormal bone metabolism including incomplete epiphyseal closure and reduction of lumbar vertebrae BMD by 3 SD, even though his testosterone level was normal. This suggests that estrogens also have a strong effect on bone metabolism in men. The results obtained in the present study are consistent with the hypothesis that hyperprolactinemia has an inhibitory effect on the hypothalamo-pituitary-gonadal axis, and the fact that estradiol was more markedly reduced than testosterone in the high PRL group indicates that estrogens may have a major effect on bone metabolism in males.

Regarding the correlations revealed by this study, there was significant negative correlation between the duration of illness and Z score in both the normal and high PRL groups. This may be interpreted as indicative of compounding factors like lack of exercise and nutritional problems in patients with schizophrenia having additional effects that result in a further decline in the Z score, i.e., a greater reduction in BMD with increased duration of the illness compared with healthy individuals. On the other hand, data from the high PRL group showed a significant negative correlation between the treatment duration and the Z score, while data from the normal PRL group showed no significant correlation between the treatment duration and the Z score. This suggests that the longer the hyperprolactinemia persists, the greater the reduction in BMD compared with normal individuals, and that there is an increased risk of reduced BMD associated with prolonged courses of treatment with agents that cause hyperprolactinemia.

It is interesting that while there was no significant correlation between the PRL levels themselves and the Z score, the duration of the treatment period (i.e., the duration of the period of high PRL levels) was correlated with the Z score in the high PRL group. Some female patients with schizophrenia experience amenorrhea as PRL levels increase to the upper limit of the normal range while others retain their normal menstrual cycles in spite of severe hyperprolactinemia, as physicians know from day-to-day clinical practice. Most probably, sensitivity to PRL differs from patient to patient, and the level of PRL does not directly reflect the extent to which bone metabolism has been affected. Alternatively, it could be that as the PRL level that inhibits the hypothalamus is reached in each patient, the organs downstream are affected, causing a reduction in BMD over time. In a report published in 1986 on 18 male patients who had prolactin-secreting pituitary tumors, Greenspan et al.[23] stated that the patients with tumors showed a significant reduction in BMD compared with age-matched control subjects, and that bone loss was related to the duration of the hyperprolactinemia and not absolute prolactin level. The results obtained in the current study are in agreement with those reported by Greenspan et al.[23]

Although the hypothalamo-pituitary-gonadal axis is basically the same in males and females, the hormone levels are very different, and therefore the effects on bone metabolism are also expected to be different. In females, the "big event" of menopause has a major effect on bone metabolism. Only males were included in the present study, in order to eliminate the menopause factor, and there were a large number of subjects. It is perhaps because of this that we could detect the effects of PRL on bone metabolism reported here.

Osteoporosis is a disease affected not only by aging and gender but also by such factors as exercise and exposure to sunlight. In the present study, the effects of these latter factors were also analyzed. In terms of exposure to sunlight, most of the subjects showed no lack of VitD.

As an index of the amount of exercise the subjects undertook, the average number of steps per day was used. Because regular daily exercise is known to prevent low BMD,[24] it is easy to imagine that a decline in the amount of exercise is related to low BMD in patients with schizophrenia. Therefore, assessing the amount of exercise is critical to an analysis of the mechanisms of reduced BMD in such patients. However, practically it is often quite difficult to thoroughly assess the amount of exercise undertaken by patients with schizophrenia. For instance, hospitalized chronic patients with schizophrenia who are asked to engage in one half hour to one hour of exercise a day often remain in bed the rest of the day. Furthermore, among patients who do not engage in recreational activity or exercise at the hospital, there are some who are quite active and have many opportunities to leave the hospital. From this perspective, we considered that an assessment of the total amount of exercise in one day by means of a pedometer would be the most suitable means of determining the level of exercise undertaken in these patients. In this study, no significant differences among the 3 exercise groups (low, medium, and high) were found. However, it must be noted that an accurate assessment of the total amount of exercise requires detailed questioning about daily behavior and calculations,[25] and merely measuring the number of steps per day with a pedometer might not have provided an adequate assessment of the total amount of daily exercise.

A limitation of this study is that the subjects' blood PRL levels were measured only once. Most of the study subjects had undergone long-term hospitalization during which the symptoms and treatments had not changed much; however, changes in medication had occurred during the long treatment periods in some cases. Thus, it is possible that the PRL levels had changed as a result of such modifications. A second limitation is that there were only 10 subjects in the normal PRL group. Although a significant difference in estradiol levels was seen in this group, it is quite possible that significant differences could also have been seen in FSH and LH levels if there had been more subjects. A final limitation is that although DEXA was used for measuring BMD, the measurements were made only on the distal one third of the radius. Because Japanese people in general tend to dislike radiation exposure, we used a relatively small instrument to measure BMD only in the radius. The lumbar vertebrae L1–L4, the femoral neck, and the trochanteric and intertrochanteric regions of the left hip are the standard sites for DEXA scans. Some may feel that measurements on the radius alone are insufficient for evaluating BMD. However, even the distal radius is representative to some degree of the bone mass of the vertebrae and the femur[26] and are not affected very much by deformation, fracture, or spur formation. Because the objective of the study was to investigate the long-term effects of PRL on bone in patients with schizophrenia, we can say that the site of the measurement would have had very little effect.

The present study has generated information on the effect of PRL levels on BMD in male patients with schizophrenia. We hope that similar studies on female patients with schizophrenia and further studies on general prevention and treatment of osteoporosis in patients with schizophrenia will now be undertaken.

Drug names: aripiprazole (Abilify), carbamazepine (Equetro, Carbatrol, and others), lithium carbonate (Eskalith, Lithobid, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), sodium valproate (Depacon and others).

REFERENCES

1. Baastrup PC, Christiansen C, Transbol I. Calcium metabolism in schizophrenic patients on long-term neuroleptic therapy. Neuropsychobiology 1980;6:56–59
2. Halbreich U, Rojansky N, Palter S, et al. Decreased bone mineral density in medicated psychiatric patients. Psychosom Med 1995;57:485–491
3. Bilici M, Cakirbay H, Guler M, et al. Classical and atypical neuroleptics, and bone mineral density, in patients with schizophrenia. Int J Neurosci 2002;112:817–828
4. Meaney AM, Smith S, Howes OD, et al. Effects of long-term prolactin-raising antipsychotic medication on bone mineral density in patients with schizophrenia. Br J Psychiatry 2004;184:503–508
5. Kishimoto T, Watanabe K, Takeuchi H, et al. Bone mineral density measurement in female inpatients with schizophrenia. Schizophr Res 2005;77:113–115
6. Halbreich U, Kinon BJ, Gilmore JA, et al. Elevated prolactin levels in patients with schizophrenia: mechanisms and related adverse effects. Psychoneuroendocrinology 2003;28(suppl 1):53–67
7. Hummer M, Malik P, Gasser RW, et al. Osteoporosis in patients with schizophrenia. Am J Psychiatry 2005;162:162–167
8. World Health Organization. Guidelines for Preclinical Evaluation and Clinical Trials in Osteoporosis. Geneva, Switzerland: World Health Organization; 1998
9. Togo T, Iseki E, Shoji M, et al. Prolactin levels in schizophrenic patients receiving perospirone in comparison to risperidone. J Pharmacol Sci 2003;91:259–262
10. DeLeon A, Patel NC, Crismon ML. Aripiprazole: a comprehensive review of its pharmacology, clinical efficacy, and tolerability. Clin Ther 2004;26:649–666
11. Maguire GA. Prolactin elevation with antipsychotic medications: mechanisms of action and clinical consequences. J Clin Psychiatry 2002;63(suppl 4):56–62
12. Iwasa T, Matsuzaki T, Tanaka N, et al. Clinical efficacy of serum LH, FSH, and PRL assay system using ARCHITECT analyzer. Sanfujinka Chiryo 2003;87:243–251
13. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. Psychol Rep 1962;10:799–812
14. Inagaki A, Inada T. Dose equivalence of psychotropic drugs: 2006 version. Jpn J Clin Psychopharmacol 2006;9:1443–1447
15. Lindsay R, Silverman SL, Cooper C, et al. Risk of new vertebral fracture in the year following a fracture. JAMA 2001;285:320–323
16. Center JR, Nguyen TV, Schneider D, et al. Mortality after all major types of osteoporotic fracture in men and women: an observational study. Lancet 1999;353:878–882
17. O'Keane V, Meaney AM. Antipsychotic drugs: a new risk factor for osteoporosis in young women with schizophrenia? J Clin Psychopharmacol 2005;25:26–31

18. Becker D, Liver O, Mester R, et al. Risperidone, but not olanzapine, decreases bone mineral density in female premenopausal schizophrenia patients. J Clin Psychiatry 2003;64:761–766
19. Abraham G, Paing WW, Kaminski J, et al. Effects of elevated serum prolactin on bone mineral density and bone metabolism in female patients with schizophrenia: a prospective study. Am J Psychiatry 2003;160:1618–1620
20. Ganong WF. Review of Medical Physiology. 22nd ed. New York, NY: Lange Medical Books/McGraw-Hill; 2005
21. Finkelstein JS, Klibanski A, Neer RM, et al. Osteoporosis in men with idiopathic hypogonadotropic hypogonadism. Ann Intern Med 1987;106: 354–361
22. Smith EP, Boyd J, Frank GR, et al. Estrogen resistance caused by a mutation in the estrogen-receptor gene in a man. N Engl J Med 1994;331: 1056–1061
23. Greenspan SL, Neer RM, Ridgway EC, et al. Osteoporosis in men with hyperprolactinemic hypogonadism. Ann Intern Med 1986;104:777–782
24. Prince RL, Smith M, Dick IM, et al. Prevention of postmenopausal osteoporosis: a comparative study of exercise, calcium supplementation, and hormone-replacement therapy. N Engl J Med 1991;325:1189–1195
25. Ainsworth BE, Haskell WL, Leon AS, et al. Compendium of physical activities: classification of energy costs of human physical activities. Med Sci Sports Exerc 1993;25:71–80
26. Trivitayaratana W, Trivitayaratana P. The accuracy of bone mineral density at distal radius on non-forearm osteoporosis identification. J Med Assoc Thai 2001;84:566–571