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Duration of the untreated period affects bone mineral density in psychiatric patients requiring long-term hospitalization: A cross-sectional study

Itsuka Kaga MD[1,2] | Hiroyoshi Iwata MD, MSc[3] | Akihiro Tokushige MD, PhD[3,4] | Takushiro Akata MD, PhD[2] | Shinichiro Ueda MD, PhD[1,3]

[1]Department of Clinical Research and Quality Management, University of the Ryukyus Graduate School of Medicine, Okinawa, Japan

[2]Department of Psychiatry, Gunma Prefectural Psychiatric Medical Center, Isesaki, Japan

[3]Department of Clinical Pharmacology and Therapeutics, University of the Ryukyus Graduate School of Medicine, Okinawa, Japan

[4]Department of Prevention and Analysis of Cardiovascular Diseases, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan

Correspondence
Itsuka Kaga, MD, Department of Psychiatry, Gunma Prefectural Psychiatric Medical Center, 2-2374 Kunisada-cho, Isesaki, Gunma 379-2221, Japan.
Email: k178761@eve.u-ryukyu.ac.jp

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Abstract

Aim: Osteoporosis and bone fractures occur often on psychiatric wards. Although recent studies showed that bone mineral density (BMD) decreases in psychiatric patients, many risk factors remain unknown. This study aimed to explore the risk factors for decreased BMD in long-term psychiatric inpatients in a closed ward.

Methods: A cross-sectional study of psychiatric inpatients hospitalized for over 20 weeks was conducted. Patients were divided into three groups according to BMD: normal, osteopenia, and osteoporosis. Psychiatric symptoms were assessed using the Brief Psychiatric Rating Scale (BPRS). The relevant history of psychiatric diseases was collected, and biomarkers related to osteoporosis were measured. Univariable and multivariable ordinal logistic regression analyses were performed to identify variables significantly associated with BMD category. Additional analyses evaluated the associations between an identified clinical variable and biomarkers and psychiatric symptoms that may be related to osteoporosis.

Results: Seventy-one patients (28 normal BMD, 17 osteopenia, and 26 osteoporosis) participated in the study. The multivariable ordinal logistic analysis showed that the duration of untreated psychosis (DUP) was a risk factor (odds ratio = 0.77, 95% confidence interval: 0.63–0.91, $p = 0.006$), adjusting for the major confounders of sex and age. Additional analysis showed significant differences in BPRS, BPRS Negative Symptom score, and the Cu/Zn ratio between the short-DUP group (DUP ≤ 1 year) and the long-DUP group (DUP > 1 year).

Conclusion: The DUP may affect BMD in long-term psychiatric inpatients, presumably partly through increased severity of negative symptoms and micronutrient abnormalities. Shortening the untreated period might reduce the risk of osteoporosis.

KEYWORDS
copper, osteoporosis, schizophrenia, time-to-treatment, zinc

INTRODUCTION

Patients with psychiatric disorders, such as schizophrenia, depression, and dementia, are at high risk of osteoporosis and consequent fractures,[1–4] yet they often go untreated because of difficulties in diagnosis and treatment,[5] resulting in impaired quality of life. Therefore, prevention of osteoporosis and bone fractures is crucial in such patients.

Japan has a large number of psychiatric beds, 72.5% of which are in closed wards.[6] The Organization for Economic Co-operation and Development (OECD) Health Statistics 2015 also showed that the length of psychiatric hospitalization was less than 1 month in major European countries, but 285 days in Japan.[7] It is conceivable that patients staying in closed wards for long periods of time are often elderly and at high risk of falls and fractures, due in part to muscle weakness and long-term medication. However, most studies of osteoporosis in psychiatric patients have been conducted in outpatients or short-term inpatients. To the best of our knowledge, few studies have included long-term inpatients in closed wards and have reported the predictors of osteoporosis in hospitalized patients; and the interventions to perform in these cases are not well understood. These concerns prompted us to study osteoporosis in relatively elderly long-term hospitalized psychiatric patients.

Reduced bone mineral density (BMD), the most important biomarker of osteoporosis, has been shown to be associated with psychiatric disorders, such as schizophrenia,[1] depression,[8] and dementia.[4] Abnormal hormone levels, such as elevated prolactin levels[8] caused by antipsychotic drugs, have been reported as a cause. However, several of the biomarkers reported to be associated with lower BMD in the general population have not been adequately examined in psychiatric patients. For example, elevations in interleukin-6 (IL-6)[9] and high-sensitivity C-reactive protein (hsCRP),[10] which represent chronic inflammation, and Cu/Zn,[11] which represents inadequate nutritional status, have not been examined.

On the other hand, it has also been reported that the severity of psychiatric symptoms significantly affects BMD loss in each disease.[8,12,13] Because BMD changes over time, the history of previous psychiatric treatment is an important factor, in addition to the assessment of current psychiatric symptoms. It has been reported that disease duration, treatment period, and the amounts of antipsychotic drugs are significantly associated with lower BMD in patients with schizophrenia when comparing osteoporosis and reduced-BMD groups with a normal group.[8] In depression, patients with a history of antidepressant treatment have a significantly reduced risk of lower BMD than those without.[14] However, few studies have focused on the detailed description of the treatment history of psychiatric disorders, such as duration of untreated psychosis (DUP) and age of onset.

The primary aim of the present study was to determine the incidence of osteoporosis in long-term hospitalized patients on a closed psychiatric ward and to perform an exploratory assessment of its associations with medical history (onset age, treatment start age, disease duration, treatment period, duration of untreated period) and with biochemical markers relevant to the risk of osteoporosis, such as hsCRP, IL-6, Cu, and Zn.

METHODS

Study design

A single-center, cross-sectional study was carried out.

Study setting

The study was conducted at the Gunma Prefectural Psychiatric Medical Center (Isesaki, Gunma, Japan) from April 2019 to October 2020.

Participants

Patients aged 50 years and over with a diagnosis of F0–F9 psychiatric disorders as defined in the 10th revision of the *International Statistical Classification of Diseases and Related Health Problems* (ICD-10)[15] who were hospitalized in closed wards of the Gunma Prefectural Psychiatric Medical Center for more than 20 weeks participated in the present study. Patients with a history of a disease or medication that affects BMD, such as metastatic or advanced cancer, prostate cancer, severe liver and renal diseases, Paget's disease, osteomalacia, hyperthyroidism, systemic steroids, heparin, phenytoin, phenobarbital, methotrexate, estrogen, testosterone, calcium and vitamin D supplementation, calcitonin, bisphosphonate, selective estrogen modulator, parathyroid hormone, and RANK ligand inhibitors were excluded. Patients who were unable to remain at rest during BMD measurement due to psychiatric symptoms were also excluded.

Diagnosis and assessment of psychiatric diseases

Each patient was diagnosed based on consensus by at least two psychiatrists according to the ICD-10 criteria. If the patient had multiple diagnoses, the disease that was the main reason for his or her hospitalization was selected. Onset age was the age at which the diagnostic criteria for each disease of the ICD-10 were met. Treatment start age was the age at which the patient started continuous treatment. DUP was the period from the onset age to the treatment start age. Disease duration was the period from the onset age to the age at participation in this study. The treatment period was the period from the treatment start age to the age at participation in this study. However, if treatment was interrupted for 1 year or more, that period was excluded from the treatment period. The duration of hospitalization was the number of months from this hospitalization to participation in the clinical trial. If the patient was temporarily transferred to another hospital to treat a physical illness, it was

considered a continued hospitalization. The period of isolation represented the number of days that the patient required treatment in an isolation room during the year immediately preceding the measurement date. The total length of hospitalization in the past was the cumulative months of hospitalization in the psychiatric ward, excluding this hospitalization. Psychiatric symptoms were assessed by three specialists, all certified psychiatrists of the Japanese Board of Psychiatry and designated physicians of mental health, using the Brief Psychiatric Rating Scale (BPRS). The Japanese version of the Oxford variation of the BPRS by Kitamura et al. was used.[16] The Negative Symptoms subscale was evaluated by the total score of four of 18 items: emotional withdrawal, motor retardation, uncooperativeness, and blunted affect.[17]

Outcome measure: BMD

BMD of the forearm was measured by dual-energy X-ray absorptiometry (Dichroma Scan DCS-600 EXV, Hitachi Aloka Medical, Ltd). The *T* score was expressed as standard deviation (SD) units compared with the average value for young healthy women. *T* scores can fall as low as −1 SD and still be considered healthy. Patients with *T* scores between −1 and −2.5 SD are diagnosed with osteopenia and are considered at high risk for osteoporosis. Patients with *T* scores lower than −2.5 SD are diagnosed with osteoporosis.[18] The World Health Organization (WHO) has recommended dividing osteoporosis into "normal," "osteopenia," "osteoporosis," and "severe osteoporosis" as diagnostic categories based on the relation between BMD values and fracture incidence in the general population. As there were only two subjects in the most severe category in the present study, and as the criteria for "osteoporosis" and "severe osteoporosis" differed only by the presence or absence of fragility fractures and not in *T* scores, these two groups were combined into the "osteoporosis" group, and the subjects were divided into three groups for analysis. This may be clinically meaningful because orthopedic practice follows these three categories, rather than considering BMD itself.

Sample collection and storage for the measurement of biomarkers

Blood and urine samples were collected at 8 a.m. after overnight fasting. Blood was drawn into vacutainer tubes, placed immediately on ice, allowed to clot for at least 30 min, and centrifuged at 3500 *g* for 15 min at 4°C. The obtained serum was aliquoted, transferred into polypropylene tubes containing 0.01% (m/v) sodium, and stored at −80°C until assayed. Type 1 procollagen N-terminal propeptide (total P1NP) and prolactin were assayed using an electrochemiluminescence immunoassay. Interleukin-6 (IL-6) and 25-dihygroxyvitaminD (25OHVitD) were assayed using a chemiluminescent enzyme immunoassay. Cu and Zn measurements were performed using a colorimetric method. The other blood chemistry tests were assayed using standard laboratory techniques.

Statistical analysis

An Excel database was established. All analyses were conducted using JMP Pro (Version 15) for MAC OS (Version 11.4). A two-sided p value < 0.05 was considered significant.

Descriptive statistics

The Kruskal–Wallis test and Fisher's exact test were used to examine the factors affecting BMD loss. Sex was reported as a percentage. Means and standard deviations are given for the other continuous variables. If the distribution was skewed, the median, lower quartile, and upper quartile are reported. Significant differences in continuous variables were tested using the Kruskal–Wallis test, and Fisher's exact test was used for categorical variables, comparing the distribution among the three BMD groups.

Univariable and multivariable ordinal logistic regression analyses

Univariable ordinal logistic regression analysis was performed with the variables that were significantly different on descriptive statistics. A multivariable ordinal logistic regression analysis was performed to explore new predictors, including DUP, of BMD decrease and osteoporosis, adjusting for significant confounders (age and sex), and the odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.

The limited number of cases in the analysis required careful selection of confounders for the regression analysis. Whereas there is no established rule for the numbers needed for multivariable ordinal logistic regression, the one in ten logistic rules were followed.[19] Given that the number of events, osteoporosis alone and combined events (osteoporosis and osteopenia) were 28 and 45, respectively, three variables were considered appropriate. Next, of the many variables affecting BMD, age and sex were indispensable major clinical confounders,[20] and they were therefore included in the regression model.

Biomarkers in the long- and short-DUP groups

Since the mean and median values diverged due to the skewed distribution of DUPs, participants were categorized into two groups according to the median DUP (1 year): short-DUP group, DUP ≤ 1 year; and long-DUP group, DUP > 1 year. Significant differences in continuous variables (BPRS, BPRS Negative Symptom score, Cu/Zn ratio, hsCRP, and IL-6) were tested by a non-parametric test (Wilcoxon rank–sum test), comparing the distribution of the two DUP groups.

RESULTS

Patients' characteristics

A total of 75 patients (47 males and 28 females) met the protocol requirements, of which four were excluded; thus, 71 (43 males and 28 females) were included in the analysis. As reasons for exclusion, one had taken high-dose steroids within 6 months, and three did not agree to participate (Figure 1). The psychiatric diagnoses of the included patients were F00 Alzheimer's disease in 10 patients (14%), F20 schizophrenia in 49 patients (69%), F31 bipolar affective disorder in seven patients (10%), and F32 depressive episodes in five patients (7%).

The characteristics of the patients are shown in Table 1. Their mean age was 66.0 ± 9.2 years. Missing data were serum CTx, IL-6, hsCRP, Cu/Zn ratio, 25OHVitD, prolactin, and testosterone in 2, 2, 4, 5, 4, 7, and 13 patients, respectively. There were significant differences among the groups in sex, age, BMD, serum CTx, Cu/Zn ratio, DUP, BPRS, and BPRS Negative Symptom score.

Univariable and multivariable ordinal logistic regression analyses

Univariable ordinal logistic regression was performed for all variables listed in Table 1. The results showed that sex (OR, 0.27; 95% CI, 0.10–0.68; $p = 0.005$), age (OR, 0.92; 95% CI, 0.87–0.97; $p = 0.002$), serum CTx (OR, 0.21; 95% CI, 0.05–0.72; $p = 0.021$), Cu/Zn ratio (OR, 0.22; 95% CI, 0.06–0.68; $p = 0.022$), treatment start age (OR, 0.98; 95% CI, 0.96–1.00; $p = 0.042$), DUP (OR, 0.76; 95% CI, 0.63–0.88; $p = 0.001$), BPRS (OR, 0.90; 95% CI, 0.86–0.93; $p < 0.001$), and BPRS Negative Symptom score (OR, 0.68; 95% CI, 0.58–0.76; $p < 0.001$) were all significant, with $p < 0.05$. There were no significant differences in the duration of hospitalization or isolation.

Multivariable ordinal logistic regression analysis was performed to identify genuine causal relations adjusting for the two variables age and sex. The multivariable ordinal logistic regression showed that only DUP (OR, 0.77; 95% CI, 0.63–0.91; $p = 0.006$), BPRS (OR, 0.91; 95% CI, 0.87–0.94; $p < 0.001$), and BPRS Negative Symptom score (OR, 0.74; 95% CI, 0.66–0.83; $p < 0.001$) were significantly related to osteoporosis and osteopenia (Table 2).

Relation between the untreated period and biomarkers

When a comparative test was performed between the short-DUP group and the long-DUP group (the baseline characteristics of each group, divided into two groups by DUP, are shown in Supporting Information: Table S1), the Cu/Zn ratio was significantly increased in the long-DUP group ($p = 0.014$) (Figure 2c). On the other hand, no significant differences were observed between the two groups in IL-6 and hsCRP ($p = 0.13$ and 0.197, respectively) (Figure 2a,b).

Relation between the untreated period and psychiatric symptoms

A comparative test between the short-DUP group and the long-DUP group showed significantly higher BPRS ($p < 0.001$) and BPRS Negative Symptom score ($p < 0.001$) in the long-DUP group (Figure 2d,e).

DISCUSSION

This single-center, cross-sectional study showed for the first time that DUP is significantly associated with reduction in BMD in psychiatric patients hospitalized in a closed ward for extended periods. It was assumed that prolonged DUP may have resulted in the earlier appearance and exacerbation of negative symptoms, which are considered treatment-resistant.[21] This is likely to have adversely affected BMD via changes in lifestyle. The association between severity of disease and BMD in patients with depression[13] and schizophrenia[8] might support this assumption. The DUP was used rather than the BPRS score as the main explanatory variable in the analysis since prolonged DUP may cause negative symptom exacerbation. The longer the untreated period, the shorter the remission period of negative symptoms,[21] and the more severe they are.[22] The autistic and inattentive lifestyle caused by the worsening of negative symptoms can lead to, for example, difficulties in appropriate nutritional intake for bone formation.[23,24] Indeed, the serum Cu/Zn ratio, which might reflect inappropriate nutritional intake and frailty in the elderly,

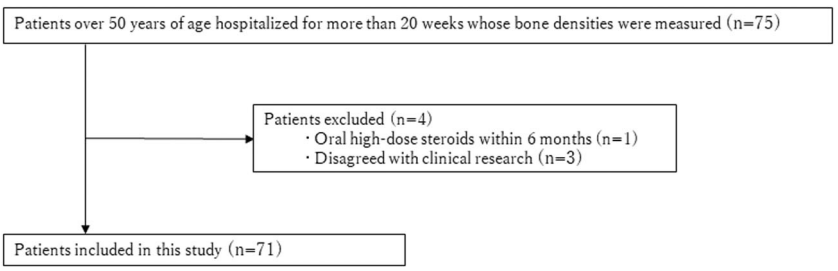

FIGURE 1 Flow profile and exclusion criteria for selection of the study population.

TABLE 1 Baseline characteristics of included patients

	All	Normal	Osteopenia	Osteoporosis	
n	71	28	17	26	*p* value
Sex (male/female) (male%)	43/28 (60.6)	20/8 (71.4)	14/3 (82.4)	9/17 (34.6)	0.003[a],*
Age (years)	66.0 (9.2)	62.3 (9.2)	65.7 (8.4)	70.2 (8.4)	0.005*
BMI (kg/m^2)	21.9 (4.1)	22.9 (4.2)	21.7 (5.1)	20.9 (3.2)	0.155
BMD (g/cm^2)	0.61 (0.14)	0.73 (0.06)	0.63 (0.05)	0.46 (0.08)	<0.001**
Total P1NP (μg/L)[b]	48.8 (35.3, 77.5)	46.3 (33.4, 67.5)	44.6 (33.4, 63.5)	64.1 (39.1, 99.5)	0.128
Serum CTx (μg/mmol/Cr)	0.63 (0.38)	0.51 (0.29)	0.62 (0.37)	0.76 (0.44)	0.044*
IL-6 (pg/mL)[b]	2.40 (1.40, 4.20)	1.75 (1.15, 3.53)	3.00 (2.00, 4.20)	2.60 (1.40, 4.30)	0.106
HsCRP (mg/dL)[b]	551 (174, 1975)	495 (165, 1740)	607 (308, 2485)	2450 (88, 18,200)	0.716
TNFα (pg/mL)[b]	0.82 (0.67, 1.01)	0.78 (0.68, 0.93)	0.90 (0.78, 1.28)	0.88 (0.62, 1.01)	0.461
Cu/Zn	1.38 (0.46)	1.23 (0.20)	1.35 (0.46)	1.57 (0.58)	0.026*
25OHVitD (ng/mL)	11.3 (4.3)	11.7 (4.3)	10.5 (4.2)	11.3 (4.5)	0.739
Prolactin (ng/mL)[b]	26.9 (10.2, 55.5)	16.7 (9.9, 46.7)	37.1 (27.5, 64.1)	28.0 (7.2, 82.1)	0.12
Testosterone (ng/mL)[b]	2.5 (0.1, 4.7)	3.7 (0.2, 4.7)	4.1 (2.9, 5.6)	0.2 (0.1, 4.1)	0.053
Period in isolation room (days)[b]	12.0 (3.0, 34.0)	14.0 (3.0, 32.0)	22.5 (17.3, 66.5)	7.0 (2.3, 14.3)	0.062
Total length of hospitalization in the past (months)[b]	6.5 (0.0, 62.8)	6.0 (0.0, 13.0)	38.0 (3.0, 100.0)	6.5 (0.0, 59.5)	0.199
Duration of hospitalization (months)[b]	8.0 (5.0, 60.5)	12.0 (5.0, 56.0)	8.0 (6.0, 102.0)	7.0 (5.0, 59.3)	0.719
Onset age (years)[b]	36.0 (22.0, 58.5)	35.5 (23.0, 51.0)	24.0 (18.0, 39.0)	54.5 (25.0, 62.8)	0.138
Treatment start age (years)[b]	36.0 (24.5, 62.5)	35.5 (24.8, 51.8)	27.0 (24.0, 46.0)	61.5 (26.0, 72.3)	0.11
Disease duration (years)[b]	24.0 (8.5, 41.0)	24.0 (3.0, 36.0)	37.0 (22.0, 44.0)	14.0 (8.0, 41.0)	0.13
Treatment period (years)[b]	23.0 (2.0, 37.5)	23.0 (2.0, 35.0)	36.0 (16.0, 41.0)	6.5 (0.5, 40.0)	0.097
Duration of untreated period (years)[b]	1.0 (0.0, 3.0)	1.0 (0.0, 1.0)	1.0 (0.0, 5.0)	2.5 (1.0, 7.3)	<0.001**
BPRS	43.8 (19.9)	27.5 (11.7)	44.5 (16.0)	60.9 (14.3)	<0.001**
BPRS Negative Symptom score	12.3 (7.5)	5.5 (0.9)	14.0 (1.2)	18.5 (1.0)	<0.001**
CP conversion (mg)[b]	400.0 (170.0, 600.0)	400.0 (187.8, 620.2)	400.0 (75.0, 600.0)	350.5 (200.0, 600.0)	0.960
CP conversion of prolactin-raising antipsychotics (mg)[b]	150.0 (0.0, 400.0)	150.5 (43.8, 400.0)	300.0 (40.0, 480.0)	43.8 (0.0, 375.0)	0.413
CP conversion of prolactin-sparing antipsychotics (mg)[b]	0.0 (0.0, 400.0)	0.0 (0.0, 525.0)	0.0 (0.0, 400.0)	75.8 (0.0, 200.0)	0.827
Biperiden conversion (mg)[b]	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.0 (0.0, 2.0)	0.0 (0.0, 0.0)	0.439
Diazepam conversion (mg)[b]	4.0 (0.0, 6.6)	2.5 (0.0, 6.6)	5.0 (0.0, 8.3)	0.0 (0.0, 5.0)	0.462

Note: The Kruskal–Wallis test was used to test for significance.

Abbreviations: 25OHVitD, 25-hydroxyvitamin D; BMD, bone mineral density; BMI, body mass index; BPRS, Brief Psychiatric Rating Scale; CP conversion, chlorpromazine conversion; CTx, C-terminal telopeptide; F, female; HsCRP, high-sensitivity C-reactive protein; IL-6, interleukin 6; M, male; P1NP, type I procollagen N-terminal propeptide; TNFα, tumor necrosis factor-alpha.

[a]Fisher's exact test.

[b]Median, lower quartile, and upper quartile are listed.

*$p < 0.05$; **$p < 0.001$.

was significantly associated with either BMD or DUP. This is consistent with a previous study showing the correlation between a high Cu/Zn ratio and impaired BMD in an elderly population.[11] The reason for the decrease in Cu/Zn despite a nearly identical diet in the hospitalization could be due to reduced or unbalanced intake, the effects of oxidative stress,[25] or impaired zinc utilization,[26] depending on strong negative symptoms.[27] Therefore, it is presumed that decreased BMD in patients with

TABLE 2 Risk factors for the BMD category on ordinal logistic regression analysis

Patient characteristic at baseline	OR	95% CI Lower	95% CI Higher	*p* value
a. Univariable associations				
Sex	0.27	0.10	0.68	0.005*
BMI (kg/m^2)	1.10	0.99	1.24	0.111
Total P1NP (μg/L)	0.99	0.98	1.00	0.098
Serum CTx (g/mmol/Cr)	0.21	0.05	0.72	0.021*
IL-6 (pg/mL)	0.94	0.81	1.07	0.376
HsCRP (mg/dL)	1.00	1.00	1.00	0.291
TNFα (pg/mL)	0.91	0.65	1.18	0.522
Cu/Zn	0.22	0.06	0.68	0.022*
25OHVitD (ng/mL)	1.02	0.92	1.13	0.774
Prolactin (ng/mL)	1.00	0.99	1.01	0.329
Testosterone (ng/mL)	1.19	0.97	1.47	0.104
Period in isolation room (days)	1.00	0.99	1.01	0.842
Total length of hospitalization in the past (months)	1.00	0.99	1.00	0.395
Duration of hospitalization (months)	1.00	0.99	1.00	0.261
Onset age (years)	0.99	0.96	1.01	0.139
Treatment start age (years)	0.98	0.96	1.00	0.042*
Disease duration (years)	1.00	0.98	1.03	0.795
Treatment period (years)	1.01	0.99	1.04	0.342
Duration of untreated period (years)	0.76	0.63	0.88	0.001*
BPRS	0.9	0.86	0.93	<0.001**
BPRS Negative Symptom score	0.68	0.58	0.76	<0.001**
CP conversion (mg)	1.00	1.00	1.00	0.58
CP conversion of prolactin-raising antipsychotics (mg)	1.00	1.00	1.00	0.877
CP conversion of prolactin-sparing antipsychotics (mg)	1.00	1.00	1.00	0.527
Biperiden conversion (mg)	1.17	0.8	1.74	0.439
Diazepam conversion (mg)	1.01	1.00	1.11	0.697
b. Multivariable associations in the final model				
Sex	0.31	0.10	0.90	0.034*
Age (years)	0.90	0.84	0.95	<0.001**
Duration of untreated period (years)	0.77	0.63	0.91	0.006*
Sex	0.39	0.11	1.31	0.129
Age (years)	0.93	0.87	0.99	0.026*
BPRS	0.91	0.87	0.94	<0.001**
Sex	0.17	0.04	0.61	0.009*
Age (years)	0.92	0.85	0.98	0.011*
BPRS Negative Symptom score	0.74	0.66	0.83	<0.001**

Abbreviations: 25OHVitD, 25-hydroxyvitamin D; 95% CI, 95% confidence interval; BMI, body mass index; BPRS, Brief Psychiatric Rating Scale; CP conversion, chlorpromazine conversion; CTx, C-terminal telopeptide; HsCRP, high-sensitivity C-reactive protein; IL-6, interleukin 6; OR, odds ratio; P1NP, type I procollagen N-terminal propeptide; TNFα, tumor necrosis factor-alpha.

*$p < 0.05$; **$p < 0.001$.

prolonged DUP is partly mediated by nutritional changes from exacerbated negative symptoms.

This study focused on the association of BMD with non-specific symptoms using the BPRS and medical history, but not with diagnosis-specific factors, because patients' symptoms varied even for the same diagnosis, or common symptoms could be present in patients with different psychiatric diagnoses. It was assumed that symptoms were what affected BMD through daily living. For example, decreased activity can be seen in the depressive state of depression, negative symptoms of schizophrenia, and apathy in dementia. In addition, since the BPRS can be conducted in a semi-structured interview and is easy to use as a screening tool, it would be clinically meaningful if psychiatric symptoms assessed by the BPRS could be used to predict osteoporosis in hospital wards.

There is evidence to suggest that antipsychotic agents affect BMD loss via prolactin and testosterone.[28] Whereas all patients but one in the present study were taking antipsychotics, the type and dose of antipsychotics, duration of treatment, and prolactin and testosterone levels were not significantly associated with decreased BMD, and the doses of sleeping pills, anxiolytics, and antiparkinsonian medications were also not significantly associated. Enhanced inflammation, which is reportedly relevant to the pathogenesis of psychiatric diseases,[29,30] might adversely affect BMD.[31] However, there was no association between any markers for inflammation and BMD in the present study.

Since BMD begins to decrease at age 50 years in both men and women in Japan,[32] it was decided to examine the degree of BMD decrease in patients aged 50 years and older. Patients who had been continuously hospitalized for more than 20 weeks were also recruited to identify factors affecting the decrease in BMD in a long-term hospitalization setting without the effects of diet and living environment prior to hospitalization and because remodeling of bone usually takes 8–20 weeks.[33] Given that the average length of hospital stay for all departments in Japan is 29.3 days,[34] and

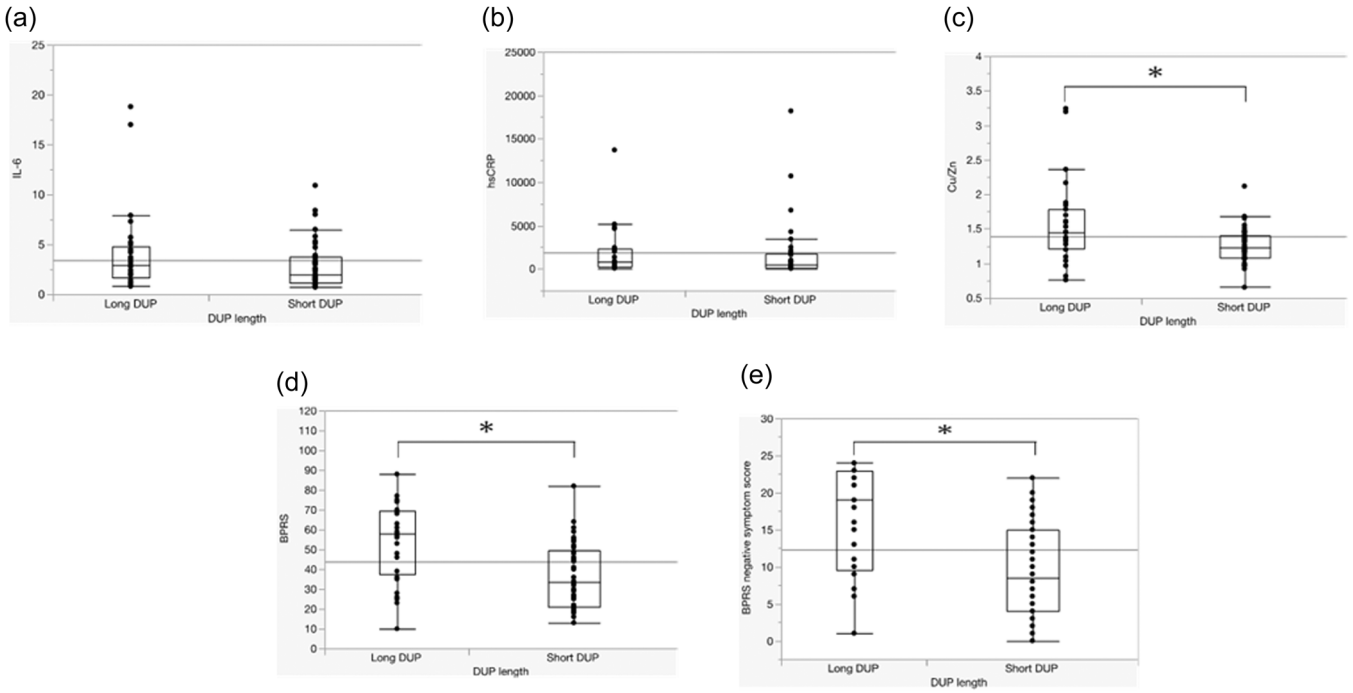

FIGURE 2 Comparisons of psychiatric evaluation scales, Cu/Zn ratio, and inflammatory markers between the long duration of untreated psychosis (DUP) group and the short-DUP group. The Wilcoxon rank–sum test was used to test for significance. (a) Interleukin-6 (IL-6; pg/mL) ($p = 0.138$). (b) High-sensitivity C-reactive protein (hsCRP; mg/dL) ($p = 0.197$). (c) Cu/Zn ratio ($p = 0.014$). (d) Brief Psychiatric Rating Scale (BPRS) ($p < 0.001$). (e) BPRS Negative Symptom score ($p < 0.001$). *$p < 0.05$.

that the length of psychiatric hospital stays in major European countries is less than 1 month, this 20-week hospital stay is considered long enough.

LIMITATIONS

There are some limitations of this study. The sample size was small because only long-term hospitalized patients at a single center were included, so the number of explanatory variables in ordinal logistic regression analysis had to be limited to three. It is necessary to validate the present results in a multicenter study with a larger sample size.

As a limitation of the measurement aspect, BMD evaluation required lumbar spine or proximal femoral density,[18] but forearm BMD was measured because many patients' psychiatric symptoms prevented measurement of other areas. However, it has been reported that there is no significant error when BMD is measured in the forearm.[35]

CONCLUSION

Various risk factors affecting decreased BMD were examined in long-term psychiatric inpatients, and it was found that DUP was a new risk factor. The present study also suggests that prolonged DUP negatively affects BMD through nutritional mechanisms and other factors, indicating the importance of early intervention for psychiatric disorders to prevent decreased BMD.

AUTHOR CONTRIBUTIONS

Itsuka Kaga was critically involved in data collection and data analysis and wrote the first draft of the manuscript. Hiroyoshi Iwata was involved in the data analysis and contributed to the interpretation of the data and the writing of the manuscript. Akihiro Tokushige was involved in the data analysis. Takushiro Akata contributed to processing and analysis of psychiatric data. Shinichiro Ueda supervised the entire project and was critically involved in the design, analysis, and interpretation of the data.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

On reasonable request, derived data supporting the findings of this study are available from the corresponding author after approval from the Ethical Committee.

ETHICS APPROVAL STATEMENT

The study protocol was reviewed and approved by the Ethics Committee of Gunma Prefectural Psychiatric Medical Center (No. 30251-69), and it was conducted according to the Helsinki Declaration of 2013.

PATIENT CONSENT STATEMENT

The study subjects were informed about the study's purpose, and written consent was obtained from each of them.

CLINICAL TRIAL REGISTRATION

N/A

ORCID

Itsuka Kaga http://orcid.org/0000-0003-2100-1806

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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