

Risk Factors for Low Bone Mineral Density Determined in Patients in a General Practice Setting

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Osteoporosis increases the risk of bone fractures. It is diagnosed based on an individual's bone mineral density (BMD) or a fracture without trauma. BMD is usually measured by the dual energy X-ray absorptiometry (DXA) method. Here we investigated factors for the earliest possible prediction of decreased BMD by examining the relationships between patients' BMD values and changes in the patients' physical and laboratory values. We retrospectively reviewed the medical records of 149 patients who visited our department in 2014-2015 for a variety of reasons and underwent an area BMD examination by DXA. We analyzed the relationships between decreasing BMD and the patients' gender, age, body mass index (BMI), medical background, hemoglobin, electrolytes, and thyroid function. Thirty-nine of the patients were diagnosed with osteoporosis based on their T-scores. An adjusted analysis showed that female gender, aging, and increased serum calcium level were significantly related to decreasing femoral BMD, whereas high BMI was associated with an increase in femoral BMD. Collectively the results indicate that for the early detection of low BMD, it is important for general-practice physicians to consider conducting a BMD checkup when treating female and elderly patients with a low BMI and/or elevated serum calcium level.

Key words: bone mineral density (BMD), body mass index (BMI), female gender, hypercalcemia, osteoporosis

The definition of osteoporosis by the World Health Organization (WHO) is based on the T-score criteria applied to bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA) measurements at the femoral neck and lumbar spine [1]. Osteoporosis is a disease that can increase the risk of fracture due to low bone mineral density (BMD) [2]. Bone fracture is further associated with an increase in mortality in the elderly [3] and is also one of the major reasons for the hospitalization of elderly individuals [4]. According to the Ministry of Health, Labour and

Welfare of Japan, healthcare costs have escalated over the past few decades along with the super-aging of Japanese society, creating a major problem for maintaining the country's universal health insurance coverage. Approximately 60% of the total national medical care expenditure is for people >65 years of age. The number of bone fractures in elderly patients has been increasing [4], and there are approximately 13 million osteoporosis patients in Japan [5]. The increase in bone fractures has also resulted in an increase in medical expenses for elderly people [6]. In order to reduce the incidence of bone fractures, efforts should be made to

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reduce the number of osteoporosis patients with low BMD.

Historically, the participation rate in osteoporosis examinations has been very low in Japan. For this reason, physicians should always consider whether patients visiting a clinic for any reason might also require an osteoporotic checkup for the detection of low BMD. In the present study, to establish a clinical hallmark for predicting low BMD in a variety of patients, we retrospectively analyzed the relationships between low BMD and various factors, including gender, body mass index (BMI), key laboratory data, treatments, and complicated diseases.

Patients and Methods

Study subjects. A total of 2,593 patients visited the Department of General Medicine, Okayama University Hospital during the period from January 2014 to December 2015. We retrospectively reviewed the medical records of 168 patients who visited the department and underwent a BMD examination during that period. Seven patients with missing body weight and height data were excluded. Twelve patients for whom the basic data of blood examination such as white blood cell count were lacking were also excluded. The data of a final total of 149 patients were analyzed (Fig. 1). The patients included 53 males (35.6%) and 96 females (64.4%), and the mean age of the patients was 58.58 years (range 19-87 years) (Table 1). As shown in Table 2, we categorized the patients into 6 groups according to their primary disorders: (1) endocrine-

metabolic disorders (Endocrine), (2) infections and inflammatory diseases (Infection), (3) neoplastic diseases (Neoplasm), (4) autoimmune-collagen disorders (Autoimmune), (5) anorexia and malnutrition (Anorexia), and (6) Others. We also divided all of the subjects into three groups by T-scores defined by WHO as follows: (1) normal range of femoral BMD (T-score ≥ -1), (2) low femoral BMD ($-2.5 < \text{T-score} < -1$), and (3) osteoporosis (T-score ≤ -2.5). Table 3 shows the numbers and ratios of patients classified by the disease categories in the three BMD-divided subgroups of normal BMD, low BMD, and osteoporosis. The study protocol was approved by the Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences and the Okayama University Hospital Ethics Committee (approval no. K1606-014).

Definition of bone strength, and laboratory and clinical examinations. We used a DXA system called the Horizon-type A (140/100 kVp, 2.5 mA, 82 sec; Hologic, Marlborough, MA, USA) at Okayama University Hospital. The area BMD measured by DXA is expressed as grams of mineral per square centimeter scanned (g/cm^2). Since the lumbar BMD in elderly patients is greatly affected by the presence of osteophytes, we used the femoral BMD values in this study. The T-score is a comparison of a patient's BMD to that of healthy young adults. Information on the patients' past medical history, clinical background, and treatments was obtained from their medical records.

Since iron-deficiency anemia [7], hyponatremia [8], loss of serum calcium and inorganic phosphorus [9], and complication of thyroid diseases [10] are known to

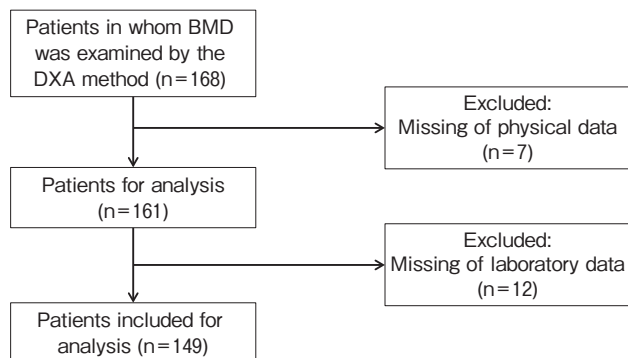


Fig. 1 Study participants. Bone mineral density (BMD) was measured in 168 patients. Seven patients were excluded because of missing physical data, and 12 patients were excluded because of missing laboratory data. The data of 149 patients were analyzed.

Table 1 Patients' characteristics (continuous variables)

		Mean	SD	Number
Age (year)		58.58	16.74	149
BMD (g/cm^2)	Femoral BMD	0.62	0.14	149
	Femoral T-score	-1.71	1.15	
BMI (kg/m^2)		22.72	5.63	149
Laboratory data	Hb (g/dL)	12.47	2.22	149
	Na (mEq/L)	138.73	3.57	147
	Ca (mg/dL)	9.48	0.66	131
	IP (mg/dL)	3.44	0.88	119
	FT4 (ng/dL)	1.15	0.25	84

BMD, bone mineral density; BMI, body mass index; Hb, hemoglobin; Na, sodium; Ca, calcium; IP, inorganic phosphorus; FT4, free thyroxine; SD, standard deviation.

be associated with osteoporosis, we analyzed each patient's blood examination data including those for hemoglobin (Hb), sodium (Na), calcium (Ca), inorganic phosphorus (IP) and free thyroxine (FT4), which were determined by an auto-analyzer system at the Central Laboratory of Okayama University Hospital. The use of heparin or warfarin [11], proton-pump inhibitors (PPIs) [12], antihypertensive drugs including angiotensin-receptor blockers [13] and loop diuretics [14], thiazolidinedione [15], benzodiazepine [16], and some psychiatric drugs such as anxiolytics, sedatives, and neuroleptics [17] have been reported to be associated with the risk of bone fractures. Taking glucocorticoids is also a potential risk factor for the development of osteoporosis [18].

Anti-diabetic DPP-4 inhibitors [19] and anti-dyslipidemic statins [20] seem to have some beneficial effect on BMD. Considering the effects of these drugs on bone metabolism, we classified the drugs administered to the patients into the following 8 groups: (1) antihypertensive drugs, (2) loop diuretics, (3) antidiabetic drugs, (4) antipsychotic/sleeping drugs, (5) anticoagu-

lants/antiplatelet drugs, (6) statins, (7) proton pump inhibitors, and (8) glucocorticoids.

Statistical analyses. The normally distributed continuous variables are presented as the mean and standard deviation (SD), and the non-normally distributed continuous variables are presented as the median and interquartile range. Categorical variables are described using proportional distributions. To estimate the effect of each variable, we performed linear regression analyses using femoral BMD as a dependent variable and the other variables as explanatory variables (crude analysis), yielding unstandardized regression coefficients (coeff.) and their 95% confidence intervals (CIs). To adjust for potential confounding, we used an adjusted model that included all variables (adjusted analysis). Some of the missing data (Na, Ca, IP, and FT4) were handled through multiple imputation by predictive mean matching [21].

We created a total of 40 imputed datasets by explanatory variables without missing values for the analysis. Values were missing for the following items: FT4 alone in 42 cases, IP and FT4 in 14 cases; Ca, IP and FT4 in

Table 2 Patients' characteristics (categorical variables)

		%	Number
Gender	Female	64.4	96
	Male	35.6	53
	Total	100.0	149
Main disease	Endocrine-Metabolic disorders	45.0	67
	Infections and inflammatory diseases	14.1	21
	Neoplastic diseases	14.1	21
	Autoimmune-Collagen disorders	11.4	17
	Anorexia and Malnutrition	6.7	10
	Others	8.7	13
	Total	100.0	149
Drugs	Proton pump inhibitors	27.5	41
	Antihypertensive drugs	26.2	39
	Antipsychotic/sleeping drugs	20.8	31
	Statins	20.8	31
	Antidiabetic drugs	12.8	19
	Glucocorticoids	11.4	17
	Anticoagulants/antiplatelet drugs	11.4	17
	Loop diuretics	6.0	9
Total	136.9*	204*	

*There might be duplicate taking. The patients were categorized into 6 groups according to their main disease: 1) Endocrine-Metabolic disorders (Endocrine), 2) Infections and inflammatory diseases (Infection), 3) Neoplastic diseases (Neoplasm), 4) Autoimmune-Collagen disorders (Autoimmune), 5) Anorexia and Malnutrition (Anorexia), and 6) others.

Table 3 Femoral T-score levels and disease category

Femoral T-score levels	Normal		Low BMD		Osteoporosis	
	T-score ≥ -1		$-2.5 < T < -1$		$T \leq -2.5$	
	Number	%	Number	%	Number	%
All patients						
Endocrine-Metabolic disorders	21	51.2	33	47.8	13	33.3
Infections and inflammatory diseases	5	12.2	11	15.9	5	12.8
Neoplastic diseases	3	7.3	10	14.5	8	20.5
Autoimmune-Collagen disorders	6	14.6	6	8.7	5	12.8
Anorexia and Malnutrition	2	4.9	4	5.8	4	10.3
Others	4	9.8	5	7.2	4	10.3
Total	41/149	100	69/149	100	39/149	100
Male only						
Endocrine-Metabolic disorders	12	57.1	7	25.9	3	60
Infections and inflammatory diseases	2	9.5	5	18.5	0	0
Neoplastic diseases	3	14.3	7	25.9	1	20
Autoimmune-Collagen disorders	3	14.3	2	7.4	1	20
Anorexia and Malnutrition	0	0	1	3.7	0	0
Others	1	4.8	5	18.5	0	0
Total	21/149	100	27/149	100	5/149	100
Female only						
Endocrine-Metabolic disorders	9	45	26	61.9	10	29.4
Infections and inflammatory diseases	3	15	6	14.3	5	14.7
Neoplastic diseases	0	0	3	7.1	7	20.6
Autoimmune-Collagen disorders	3	15	4	9.5	4	11.8
Anorexia and Malnutrition	2	10	3	7.1	4	11.8
Others	3	15	0	0	4	11.8
Total	20/149	100	42/149	100	34/149	100

Normal T-score ≥ -1 , Low BMD $-2.5 < T < -1$, Osteoporosis $T \leq -2.5$.

8 cases; Ca alone in 6 cases; IP alone in 5 cases; Ca and IP in 2 cases; Na, Ca and IP in 1 case; Na alone in 1 case; and Ca and FT4 in 1 case.

All statistical analyses were performed using Stata/MP4 ver. 15.1 (Stata Corp., College Station, TX). All *p*-values were two-sided, and *p*-values < 0.05 were accepted as significant [21].

Results

Patient characteristics of BMD, laboratory data and basal disorders. We analyzed the clinical data of patients who visited our department with various complaints. The age distributions of the patients are graphed for each gender in Fig. 2. Osteoporosis was identified in 39 (26.2%) of the 149 patients. The proportions of male and female osteoporotic patients were

12.8% and 87.2%, respectively. Our analyses revealed that the following factors in the patient profiles and physical and laboratory data were closely linked to a decrease in femoral BMD: female gender, advanced age, high BMI, and high serum calcium level. We thus consider these factors to be important for detecting osteoporosis at an early stage.

The patients' characteristics are summarized in Table 1. The mean \pm SD of femoral BMD was 0.62 ± 0.14 g/cm². The patients' laboratory data, including Hb and serum levels of Na, Ca, IP and FT4, were almost all within normal ranges (Table 1). The numbers of patients in the disease categories were as follows: Endocrine (67 patients, 45.0%), Neoplasm (21, 14.1%), Infection (21, 14.1%), Autoimmune (17, 11.4%), Anorexia (10, 6.7%), and Others (13, 8.7%). The percentage of patients with endocrine-metabolic

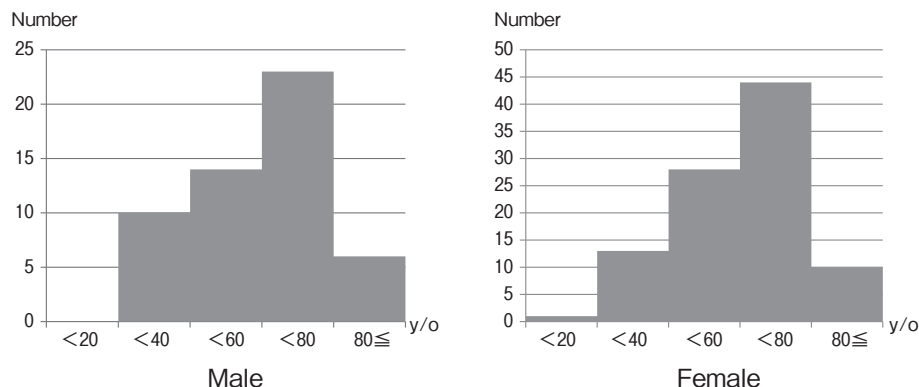


Fig. 2 Age distribution in each gender of the study population. The age distribution of female patients was skewed toward the menopausal condition, with 62 (64.5%) of the 96 women aged > 55 years.

disorders (45.0%) was highest.

The drugs administered for individual treatments are shown in Table 2. The numbers of patients in the drug-categorized groups were as follows: PPIs (41 patients, 27.5%), antihypertensive drugs (39, 26.2%), antipsychotic/sleeping drugs (31, 20.8%), statins (31, 20.8%), antidiabetic drugs (19, 12.8%), glucocorticoids (17, 11.4%), anticoagulants/antiplatelet drugs (17, 11.4%), and loop diuretics (9, 6.0%). The percentage of patients who were administered a PPI (27.5%) was the highest.

Characteristics categorized by femoral BMD levels.

As shown in Table 3, the number of patients with endocrine-metabolic diseases was the largest among the three gender-divided subgroups. Table 3 also shows the numbers and ratios of male patients classified by disease categories. In the osteoporosis group, only 5 of 39 patients were male. In the male osteoporosis subgroups, there were only three disease categories: Endocrine, Autoimmune, and Neoplasm. In contrast, there were 34 female patients with osteoporosis, among whom disorders in all 6 categories were present (Table 3).

Multiple regression analysis for factors that affect BMD. Table 4 shows the results of the linear regression analysis based on the patients' femoral BMD levels. The adjusted analysis revealed that female gender (coeff. = -0.129 , 95%CI [-0.171 , -0.088], $p < 0.0001$) was significantly associated with decreasing femoral BMD compared to male gender (Table 4). We also observed that the effect of aging, based on 10-year increments (coeff. = -0.033 , 95%CI: -0.046 to -0.019 , $p < 0.001$) was related to a decrease in femoral BMD.

Of note, higher BMI levels (coeff. = 0.005 , 95%CI: 0.002 - 0.009 , $p = 0.005$) were significantly linked to an increase in femoral BMD (Table 4). Increased serum corrected calcium levels (coeff. = -0.042 , 95%CI: -0.073 to -0.012 , $p = 0.007$) were significantly associated with a decrease in femoral BMD. In the crude analysis, only anorexia and malnutrition (coeff. = -0.115 , 95%CI: -0.209 to -0.021 , $p = 0.017$) were significantly related to low femoral BMD among the disease groups. Among the medications, the use of a PPI (coeff. = -0.063 , 95%CI: -0.114 to -0.013 , $p = 0.014$) was significantly associated with decreasing femoral BMD, though these trends were not detected in the adjusted analysis.

Since the average of the VIF statistics was 1.43 in the multiple regression analysis, multiple co-linearity was not shown. A plot of multiple linear regression analysis for factors affecting the femoral BMD levels is shown in Fig. 3, which illustrates the relationships between BMD and female gender, age, BMI, and serum calcium based on an adjusted analysis of the multiple linear regression analysis results (Table 4).

Discussion

We analyzed clinical data including BMD and laboratory data for 149 patients who visited our department during a 2-year period. Our analyses clarified that (1) female gender was significantly associated with decreasing femoral BMD compared to male gender, and (2) increased serum calcium level, (3) aging, and (4) low BMI were significantly linked to a decrease in femoral BMD.

The difference in the numbers of female and male

Table 4 Results of multiple regression analysis with femoral BMD as outcome

		Crude analysis			Adjusted analysis				
		Coef.	95%CI		<i>p</i> -value	Coef.	95%CI		<i>p</i> -value
Gender	Male	0.000	Reference			0.000	Reference		
	Female	-0.135	-0.178	-0.093	< 0.001**	-0.129	-0.171	-0.088	< 0.001**
MD	Endocrine-Metabolic disorders	0.000	Reference			0.000	Reference		
	Autoimmune-Collagen disorders	-0.025	-0.100	0.050	0.515	0.022	-0.048	0.092	0.537
	Neoplastic diseases	-0.052	-0.122	0.017	0.137	-0.027	-0.102	0.047	0.470
	Infections and inflammatory diseases	-0.032	-0.101	0.038	0.368	0.018	-0.048	0.084	0.588
	Anorexia and Malnutrition	-0.115	-0.209	-0.021	0.017*	-0.085	-0.173	0.002	0.056
	Others	-0.027	-0.111	0.057	0.531	0.002	-0.067	0.071	0.956
Age (10-year increments)		-0.029	-0.042	-0.016	< 0.001**	-0.033	-0.046	-0.019	< 0.001**
BMI		0.008	0.004	0.012	< 0.001**	0.005	0.002	0.009	0.005**
Drugs	Antihypertensive drugs	-0.018	-0.070	0.034	0.495	0.028	-0.019	0.075	0.240
	Loop diuretics	-0.014	-0.110	0.083	0.782	-0.056	-0.137	0.026	0.178
	Antidiabetic drugs	0.029	-0.039	0.098	0.398	0.011	-0.049	0.071	0.713
	Antipsychotic/sleeping drugs	-0.055	-0.111	0.001	0.052	-0.045	-0.093	0.003	0.067
	Anticoagulants/antiplatelet drugs	0.030	-0.042	0.102	0.405	0.044	-0.019	0.107	0.170
	Statins	0.004	-0.053	0.060	0.894	-0.010	-0.060	0.040	0.698
	Proton pump inhibitors	-0.063	-0.114	-0.013	0.014*	-0.049	-0.101	0.004	0.069
	Glucocorticoids	0.047	-0.025	0.118	0.201	0.031	-0.034	0.095	0.353
Labo	Hb	0.009	-0.001	0.019	0.083	-0.011	-0.021	0.000	0.053
	Na	0.001	-0.006	0.007	0.807	0.000	-0.006	0.006	0.925
	Corrected Ca	-0.022	-0.057	0.014	0.234	-0.042	-0.073	-0.012	0.007**
	IP	0.015	-0.015	0.045	0.316	0.019	-0.006	0.043	0.141
	FT4	-0.016	-0.126	0.094	0.772	-0.028	-0.118	0.061	0.531

Abbreviations: see footnotes of Table 1 and Table 2. MD, Main disease; Labo, Laboratory data. * $p < 0.05$ and ** $p < 0.01$.

osteoporotic patients indicates the possibility that female gender itself is a critical factor for BMD compared to other clinical factors. Our adjusted model revealed that female gender was significantly associated with decreasing femoral BMD compared to male gender. Regarding female gender, menopause, the natural age of which ranges from 50 to 55 years, is generally linked to a decrease of femoral BMD [22]. Since the age distribution of the female patients in our cohort was skewed to the menopausal condition (62 of the 96 women [64.5%] were aged > 55 years), it was difficult to analyze the data by dividing the women into 2 groups of pre- and post-menopausal conditions. However, female gender and aging are likely to be independently related to lowered BMD [23,24]. It has also been reported that men showed higher BMD values than women at the same age [25], suggesting that female sex hormones could be critical for the gender-dependent difference of BMD regardless of menopause. Further

prospective studies are needed to clarify the inter-relationships among gender difference, changes of sex steroids, and the existence of menopause.

We also observed that aging was significantly correlated with a decrease in femoral BMD regardless of gender. The decrease in BMD caused by aging is related to the acceleration of bone remodeling [26,27], an increase in oxidative stress [28], and decreases in calcium absorption [29] and secondary bone calcification [30]. Although we did not retrospectively analyze these factors in the present study, a BMD examination should be recommended for women aged ≥ 50 years considering the decline in estrogen in females. It has also been reported that most fractures in elderly people are at cortical sites [31], indicating the difficulty in determining the risk of bone fractures in elderly people.

A gain in BMI also had a significant relation to increasing femoral BMD in our study. It is possible that the BMI is more strongly correlated with BMD regard-

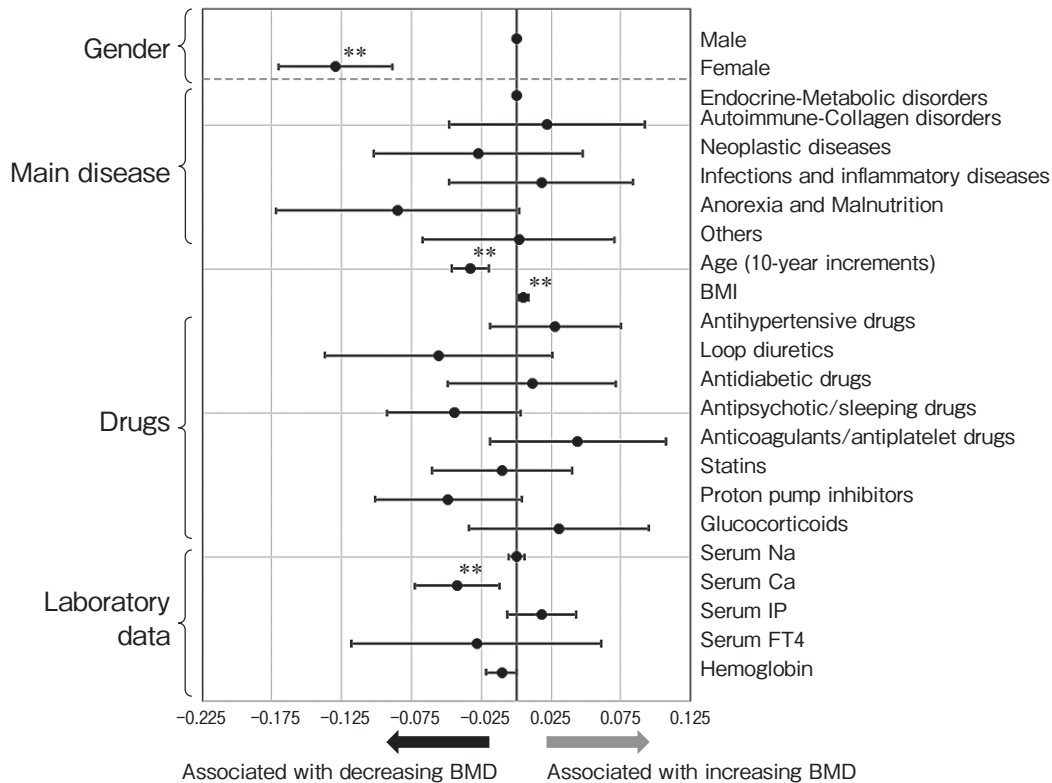


Fig. 3 Inter-relationships between clinical factors and femoral BMD. A plot of the multiple liner regression analysis results for factors that affect femoral BMD (see Table 4) is shown. The relationships between BMD and the factors of female gender, age, BMI, and serum Ca were significant. Na, sodium; Ca, calcium; IP, inorganic phosphorus; FT4, serum free thyroxine. $**p < 0.05$.

less of age or gender [32]. In this regard, reduced BMI in the elderly may be linked to frailty, which is defined as a clinical state with increased vulnerability resulting from an aging-related decline in physiologic functions involving various organs in the elderly [33]. Frailty is a syndrome including key phenotypic conditions such as weakness, slower walking speed, lower physical activity and energy, exhaustion, and unintentional weight loss [33]. Since a low BMI or weight loss in the elderly is an important component of frailty, attention should be given to the risk of lowered BMI in lean elderly people in order to avoid the development of osteoporosis.

Regarding the serum calcium level, it is generally recognized that the major causes of hypercalcemia are primary hyperparathyroidism and malignancy [34]. In our adjusted analysis, hypercalcemia was found to be significantly correlated with decreasing BMD independently of other factors, whereas the serum level of inorganic phosphate was not directly associated with BMD. There were 26 patients with hypercalcemia with

a serum calcium level > 10 mg/dL, including 16 female patients (61.5%) and 25 patients with a low BMI (≤ 20) (96.2%). Because of these factors, the relationship between hypercalcemia and decreasing femoral BMD seemed to be underestimated in our crude analysis. The adjusted analysis enabled a correct estimation of the relationship between hypercalcemia and decreasing femoral BMD. Since patients with elevated serum calcium are likely to become osteoporotic within approximately 10 years [35], hypercalcemic patients should be monitored in order to determine the causes of calcium dysregulation and to prevent the progression of osteoporosis.

In our patient cohort, other clinical factors did not directly affect decreasing BMD, including autoimmune diseases, anorexia and malnutrition, and the intake of glucocorticoids and PPIs, which would be expected to be involved in low BMD. These discrepancies might be due to the small numbers of our patients with these disorders. For example, among the 17 patients with auto-

immune-collagen disorders, only 4 had rheumatoid arthritis. Only 10 of the 149 patients had anorexia or malnutrition. Seventeen patients were taking glucocorticoids, which are known to cause osteoporosis [36, 37], and only 6 of those patients had been administered glucocorticoids for > 1 year. Thirty-three (80.5%) of the patients taking a PPI were >60 years old. These deviations in the patient numbers and distribution of ages and/or gender might have played a role in the unexpected results obtained in this study.

In addition, DXA measurements at the hip and spine are common and useful methods for diagnosing osteoporosis in daily medical practice [38]; however, high-resolution peripheral quantitative computed tomography (HRpQCT) was recently introduced to measure volumetric BMD and micro-architectural bone fractures [39]. In a future study, HRpQCT would be more advantageous for assessing cortical porosity [40].

Collectively, our present findings revealed that, in clinical practice for general medicine, female gender and aging factors are important to predict a decrease in femoral BMD. Attention should also be paid to the possibility of low BMD in patients with a high serum calcium level and/or low BMI. There were two main limitations in this study. First, this was a retrospective analysis. Approximately 95% of the patients who visited our department in 2014-2015 did not undergo a DXA examination, suggesting that risk factors for decreasing BMD might be underestimated in unexamined patients by attending physicians. Another study limitation is that the percentage of patients with endocrine diseases was higher than the percentages of patients with other diseases. Nevertheless, to prevent fractures in such patients, we should always pay attention to key clinical factors considering the possibility of decreasing BMD among individuals who visit a general medical practice.

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