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Factors Affecting Bone Mineral Density in Hemodialysis Patients with Diabetic Nephropathy

HIROSHI KAJI, SABURO HATTORI*, KENICHI SEKITA*, TOSHITSUGU SUGIMOTO AND KAZUO CHIHARA

Division of Endocrinology/Metabolism, Neurology and Hematology/Oncology, Department of Clinical Molecular Medicine, Kobe Graduate University School of Medicine, Kobe 650-0017, Japan
**Hattori Hospital, Miki 673-0413, Japan*

Abstract. Background: It remains undetermined whether bone mineral density (BMD) of hemodialysis (HD) patients with diabetes mellitus (DM) is reduced or not. The present study was performed to compare BMD between HD patients with DM and chronic glomerulonephritis (CGN). We analyzed the factors which affected BMD of 139 patients with chronic HD enrolled in this cross-sectional study. Methods: BMD of forearm [1/3-radius (R) and ultradistal (UD)-R] were measured by dual-energy x-ray absorptiometry. Results: 1/3R-BMD and UDR-BMD of DM patients were comparable to those of CGN patients. In DM patients, body mass index (BMI) was positively correlated with UDR-BMD, serum levels of PTH and creatinine were negatively correlated with 1/3R-BMD, and serum level of β2-microglobulin (βMG) was positively correlated with UDR-BMD. In CGN patients, duration of HD and height were negatively correlated with 1/3R- and UDR-BMD, serum levels of uric acid and triglyceride were positively correlated with 1/3R- and UDR-BMD, and serum level of total cholesterol was positively correlated with UDR-BMD. In stepwise regression analysis, BMI and serum levels of creatinine and βMG were selected for UDR-BMD in DM patients, although serum PTH level was selected for 1/3R-BMD. Conclusion: BMD at forearm was comparable between DM and CGN in HD patients. The factors affecting BMD seemed to be different between DM and CGN.

Key words: Bone mineral density, Hemodialysis, Diabetes mellitus, Chronic glomerulonephritis

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OSTEOPOROSIS is a serious disease affecting large numbers of older people throughout the world. The endpoint of its treatment is the prevention of bone fractures, particularly those of the hip and vertebrae. Chronic hemodialysis (HD) has become so well developed that an extended life expectancy has become possible. This in turn gives rise to various new problems relative to the quality of life in HD patients due to vertebral and femoral neck fractures. It has generally been accepted that HD patients have diminished bone mineral density (BMD). Bone abnormalities in such patients include hyperparathyroid bone disease and adynamic bone disease, and it is likely that these disorders are related to fractures. Because increasing morbidity and mortality has been noted in HD patients with nonoperated hip fractures [1], it is important to discriminate HD patients at high risk of fractures so that precautions can be taken to prevent them. It is well known that human bone mass is determined by multiple genetic and environmental factors, such as anthropometrical factors, nutrition, exercise, hormones and cytokines. The consensus for the factors predicting the fracture risk is still pending, although BMD has been considered to be a useful predictor of bone fractures. Our previous study revealed that radial BMD is useful for the prediction of fractures in HD patients [2], although several previous studies have suggested that lumbar spine (LS) BMD and femoral neck BMD

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Correspondence to: Hiroshi KAJI, M.D., Division of Endocrinology/Metabolism, Neurology and Hematology/Oncology, Department of Clinical Molecular Medicine, Kobe Graduate University School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan

were of no value for defining HD patients at risk to nonspine fractures [3–5]. Since numerous factors affect BMD, it is not easy to clarify the most important factor which determines BMD.

Diabetes mellitus (DM) and chronic glomelulonephritis (CGN) are two main causal diseases of chronic renal failure, requiring HD treatment. Previous studies revealed that patients with insulin-dependent DM and normal renal function have reduced bone mass, low bone formation rates and low parathyroid hormone (PTH) levels when compared to age-matched normal subjects [6, 7]. In HD patients, DM patients have also been noted to have lower plasma PTH levels and bone formation rates [8–10], as well as diminished parathyroid gland responsiveness to acute hypocalcemic challenge [11] when compared to non-diabetic controls. Although controversy exists as to whether BMD of patients with non-insulin-dependent DM without renal dysfunction would be reduced or increased [12–16], few reports are available about BMD of HD patients with DM [17] and the factors which determine BMD of those patients.

The present study was therefore performed to compare BMD between HD patients with DM and CGN. Moreover, we analyzed the factors which affected BMD by employing the background of patients, biochemical data, and BMD in 139 patients with chronic HD enrolled in this cross-sectional study.

Materials and Methods

Patients

Subjects were 139 Japanese patients (75 male and 64 female) on dialysis at the Hattori Hospital in Miki, Hyogo Prefecture, Japan. This study was approved by the Institute Review Board of our institution. Subjects agreed to participate in this study and gave their informed consent. They underwent HD for 6.97 ± 6.70 years (mean ± SD, range 0.1–28 years), and their underlying diseases causing uremia were CGN (n = 83) and DM (n = 56). HD treatment was performed three times a week, 3–5 h per treatment. Dialysis fluid was free of aluminium and contained 2.5 mEq/L calcium and 1.5 mEq/L magnesium. Heparin (2500–6500 units) was routinely administered during HD treatment. In addition to cardiac and antihypertensive therapy, patients received oral calcitriol at doses of 0.34 ± 0.35 μg/day (mean ± SD, 0.32 ± 0.41 for DM; 0.36 ± 0.30 for CGN) and oral calcium carbonate at doses of 2.8 ± 1.9 g/day (2.5 ± 1.8 for DM; 3.1 ± 1.8 for CGN) to maintain serum calcium concentration between 8.5 and 10.5 mg/dl and serum phosphorus concentration at levels lower than 7.0 mg/dl.

BMD

BMD of the forearm without arteriovenous fistula was measured by a technician using dual-energy x-ray absorptiometry (DXA) (Hologic QDR-1000, Waltham, MA) during January 2000 to February 2001. Separate measurements of radius (R) were done using software (Hologic QDR-1000, version 5.47Q for the forearm). Sites of the radius were 1/3 and ultradistal (UD). 1/3-R and UD-R are generally considered to be rich in cortical and trabecular bone, respectively. The same operator tested all the patients during the study to eliminate operator discrepancy. BMD was automatically calculated from the bone area (cm^2) and bone mineral content (BMC) (g) and expressed absolutely in g/cm^2. The Z-score is a percent value, by which a given measurement differs from the mean of a sex- and age-matched reference population.

Biochemical measurement

Blood samples were collected at an access vessel puncture on the first day of the week of regular HD. Serum was promptly separated and stored at −20°C until assay. Routine serum chemistry determinations were performed by standard automated techniques. Serum level of PTH was measured by an IRMA (Allegro Intact PTH-RIA kit, Nichols Institute Diagnostics) [18, 19].

Statistical analysis

Data were expressed as mean ± standard deviation (SD) for each group. Comparisons between groups were made with the nonparametric Mann-Whitney U-test. The regression analysis was performed using the statistical computer program Statview (Abacus Concepts, Inc., Berkeley, CA). Single regression analysis was used to assess the linear relationship between study parameters, and then Pearson's correlation coefficients were calculated. In order to determine which variables were independently related to BMD,

stepwise regression analysis was performed. P-value less than 0.05 was considered to be significant.

Results

Descriptive data

BMD data at R of HD patients with DM and CGN are shown in Table 1. 1/3R-BMD and UDR-BMD of DM patients were comparable to those of CGN patients. A similar tendency was observed about Z-score. We next compared DM and CGN in each gender. In both male and female patients, BMD at all sites were comparable between DM and CGN patients. 1/3R-BMD and UDR-BMD of DM patients were similar to those of both male and female CGN patients, even when the durations of HD in both groups were matched (Table 2).

Correlation coefficients of BMD

We analyzed the correlation coefficients of BMD (Z score) at various sites with various indices [duration of HD, height, body weight, BMI, serum levels of calcium, phosphorus, calcium × phosphorus, ALP, PTH, calcitonin, blood urea nitrogen (BUN), creatinine, uric acid, total cholesterol, triglyceride, sodium, potassium, ALT, AST, hematocrit, β2-microglobulin (βMG), iron, ferritin, cholinesterase and LDH, oral calcium and calcitriol dose]. The correlation coefficients of BMD at various sites with various indices in DM and CGN patients are shown in Tables 3 and 4, respectively. Some other variables which were not significantly related to BMD at any site are not shown in the Tables.

In DM patients, BMI was positively correlated with UDR-BMD. Serum levels of PTH and creatinine were negatively correlated with 1/3R-BMD. Serum level of βMG was positively correlated with UDR-BMD. In male patients with DM, serum level of uric acid ($r = -0.357$, $p = 0.0484$) was correlated with 1/3R-BMD and body weight was correlated with UDR-BMD ($r = 0.363$, $p = 0.0442$). In female patients with DM, serum levels of PTH ($r = -0.472$, $p = 0.0295$) and ALT ($r = 0.442$, $p = 0.0439$) were correlated with 1/3R-BMD, and body weight ($r = 0.464$, $p = 0.0329$) and

Table 1. Comparison of BMD between DM and CGN patients

	Total		Male		Female	
	DM	CGN	DM	CGN	DM	CGN
Number of patients	56	83	32	43	24	39
1/3R-BMD (g/cm²)	0.584 ± 0.097	0.559 ± 0.116	0.633 ± 0.057	0.630 ± 0.069	0.513 ± 0.099	0.483 ± 0.108
1/3R-BMD (Z score)	90 ± 15	87 ± 15	86 ± 10	84 ± 11	96 ± 19	91 ± 19
UDR-BMD (g/cm²)	0.375 ± 0.080	0.357 ± 0.084	0.399 ± 0.069	0.401 ± 0.076	0.340 ± 0.083	0.310 ± 0.064
UDR-BMD (Z score)	92 ± 19	88 ± 17	87 ± 15	83 ± 16	100 ± 23	94 ± 17

Values are expressed as mean ± SD.

Table 2. Comparison of BMD between DM and CGN patients in each gender (duration of HD matched)

	Total		Male		Female	
	DM	CGN	DM	CGN	DM	CGN
Number of patients	51	49	28	30	23	19
Age (year)	66.7 ± 9.7	65.3 ± 12.5	68.9 ± 7.4	65.3 ± 12.6	64.0 ± 11.5	65.3 ± 12.7
Duration of HD (year)	4.1 ± 2.7	4.1 ± 2.6	4.2 ± 2.8	4.1 ± 3.1	4.0 ± 2.6	4.2 ± 1.8
Body mass index	21.2 ± 2.7	20.5 ± 2.6	21.2 ± 2.5	21.0 ± 2.6	21.2 ± 3.1	19.4 ± 2.4
1/3R-BMD (g/cm²)	0.578 ± 0.098	0.588 ± 0.110	0.629 ± 0.059	0.641 ± 0.072	0.513 ± 0.099	0.504 ± 0.108
1/3R-BMD (Z score)	90 ± 15	90 ± 15	85 ± 10	86 ± 11	96 ± 19	97 ± 19
UDR-BMD (g/cm²)	0.372 ± 0.080	0.369 ± 0.084	0.398 ± 0.070	0.402 ± 0.080	0.340 ± 0.083	0.317 ± 0.063
UDR-BMD (Z score)	92 ± 20	89 ± 18	86 ± 15	84 ± 17	100 ± 23	99 ± 15

Values are expressed as mean ± SD.

BMI ($r = 0.462$, $p = 0.0394$) were correlated with UDR-BMD.

In CGN patients, duration of HD and height were negatively correlated with 1/3R- and UDR-BMD. Serum levels of uric acid and triglyceride were positively correlated with 1/3R- and UDR-BMD. Serum level of cholesterol was positively correlated with UDR-BMD. In male patients with CGN, duration of HD ($r = -0.446$, $p = 0.0031$) as well as serum levels of uric acid ($r = 0.358$, $p = 0.0192$) and cholinesterase ($r = 0.310$, $p = 0.0453$) were correlated with 1/3R-BMD, while body weight ($r = 0.397$, $p = 0.0087$), BMI ($r = 0.397$, $p = 0.0087$) and serum levels of calcium ($r = -0.313$, $p = 0.0431$), urea nitrogen ($r = 0.350$, $p = 0.0225$), uric acid ($r = 0.359$, $p = 0.0188$) and triglyceride ($r = 0.353$, $p = 0.0212$) were correlated with UDR-BMD. In female patients with CGN, duration of HD ($r = -0.404$, $p = 0.0154$) and serum levels of uric acid ($r = 0.349$, $p = 0.0396$) and potassium ($r = -0.369$, $p = 0.0285$) were correlated with 1/3R-BMD, while the duration of HD ($r = -0.383$, $p = 0.0225$) and serum level of potassium ($r = -0.342$, $p = 0.0441$) were correlated with UDR-BMD.

Table 3. Correlations between BMD and various indices in DM patients

Z score	1/3R-BMD		UDR-BMD	
	r	p	r	p
Duration of HD	−0.098	0.4957	0.009	0.9479
ALP	−0.168	0.2386	−0.148	0.3027
PTH	−0.299	0.0327*	−0.167	0.2440
Height	−0.245	0.0800	−0.169	0.2328
Body mass index	−0.017	0.9076	0.403	0.0028*
Creatinine	−0.287	0.0388*	−0.152	0.2830
Uric acid	−0.196	0.1654	−0.126	0.3763
Total cholesterol	0.081	0.5698	0.200	0.1565
Triglyceride	0.064	0.6557	0.228	0.1044
β2-microglobulin	0.207	0.2072	0.326	0.0421*
BUN	−0.068	0.6349	0.095	0.5033
HbA_{1c}	−0.174	0.2281	−0.042	0.7734
Oral calcitriol dose	0.036	0.8014	−0.016	0.9127
Oral calcium dose	0.027	0.8490	0.118	0.4053

*$p<0.05$

Table 4. Correlations between BMD and various indices in CGN patients

Z score	1/3R-BMD		UDR-BMD	
	r	p	r	p
Duration of HD	−0.359	0.0012*	−0.252	0.0266*
ALP	−0.171	0.1354	−0.100	0.3867
PTH	−0.060	0.6000	0.009	0.9412
Height	−0.225	0.0484*	−0.278	0.0139*
Body mass index	0.080	0.4909	0.207	0.0712
Creatinine	−0.025	0.8329	−0.020	0.8632
Uric acid	0.342	0.0021*	0.249	0.0276*
Total cholesterol	0.118	0.3088	0.326	0.0036*
Triglyceride	0.236	0.0373*	0.304	0.0066*
β2-microglobulin	0.067	0.5890	0.148	0.2301
BUN	0.027	0.8143	0.158	0.1663
Oral calcitriol dose	−0.019	0.8679	0.048	0.6831
Oral calcium dose	−0.032	0.7835	−0.109	0.3433

*$p<0.05$

Factors affecting BMD

In order to determine which variables were independently associated with BMD in DM and CGN patients, stepwise regression analysis describing BMD was performed including duration of HD, height, BMI, serum levels of ALP, PTH, creatinine, uric acid, total cholesterol, triglyceride and βMG as independent variables. The equations applied to each regional BMD are shown in Table 5. As for DM patients, serum level of PTH was selected for 1/3R-BMD. BMI as well as serum levels of creatinine and βMG were selected for UDR-BMD. As for CGN patients, duration of HD was selected for 1/3R-BMD, and serum levels of uric acid and triglyceride were selected for UDR-BMD.

Table 5. Stepwise multiple regression analysis against BMD

	BMD region	Equations	Model R^2
DM	1/3R	98.011 −0.063 × PTH	0.143
	UDR	36.035 +3.929 × BMI −3.630 × Cr +0.313 × βMG	0.416
CGN	1/3R	65.636 −0.573 × Duration of HD +3.162 × UA	0.180
	UDR	77.336 +0.084 × TG	0.099

βMG: β2-microglobulin; BMI: body mass index; Cr: creatinine; UA: uric acid; TG: triglyceride
Independent variables: Duration of HD, height, BMI, serum levels of ALP, PTH, Cr, UA, total cholesterol, TG and βMG
Dependent variables: BMD (% age matched)

The fraction of variance explained by these equations (R^2) ranged from 0.099 in UDR-BMD of CGN patients to 0.416 in UDR-BMD in DM patients. Factors affecting BMD were differed, depending on the site measured and underlying disease.

Discussion

Type I DM patients with normal renal function have reduced bone mass, low bone formation rates, and low plasma PTH concentrations, as compared to age-matched normal subjects [7, 20]. In contrast, numerous studies indicated that bone mass was undiminished or even increased in patients with type II DM [12–16]. The present study revealed that BMD were comparable between DM and CGN in HD patients. Even when we compared BMD between DM and CGN by using subjects whose durations of HD and age were matched, a similar tendency was observed. In previous studies, the concentrations of creatinine and PTH were lower in HD patients with DM, compared to those with non-DM [7], and DM was one of the independent risk factors for the aplastic bone disorder [21]. Moreover, Nishitani *et al.* [17] reported decreased BMD at the third lumbar vertebra, head, pelvis and whole body in diabetic patients on HD. However, BMD of DM patients were comparable, compared to those of CGN patients in the present study. The reason for these discrepancies is unknown, but it might be partly explained by the differences in the sites measured. Our previous study [2] suggested that radial BMD was useful to separate the patients with or without fractures. Therefore, BMD at the sites closely related to fractures might not be reduced in HD patients with DM. Our previous studies [2, 22] indicated that LS-BMD is not useful to predict fractures in HD patients, mainly due to the calcification of aorta. Alternatively, LS-BMD might not be useful, partly because the vertebral body in HD patient often shows a heterogenous density and becomes osteosclerotic, which results in higher BMD. These findings suggest that LS-BMD is not useful for the diagnosis of osteoporosis and renal osteodystrophy in HD patients.

In the present stepwise multiple regression analysis, BMI as well as serum levels of PTH, creatinine and βMG were selected as the factors, which affected BMD of DM patients. On the other hand, duration of HD as well as serum levels of uric acid and triglyceride were selected in CGN patients. Moreover, different factors affected BMD when analyzed separately in male and female patients. These data suggested that factors, which affect BMD, are different between DM and CGN, and that the different factors affect BMD depending on measured site and gender. The reason why the determinants of BMD are different in DM and CGN is unknown. DM patients are in various metabolic states and are complicated by numerous disorders due to DM, and several parameters including duration of HD, serum levels of calcium, PTH, creatinine, uric acid and cholesterol were different between DM and CGN (data not shown). Taken together, HD duration, calcium metabolism or nutritional state might affect the difference between DM and CGN.

Serum PTH level was negatively correlated with 1/3R-BMD and a negative predictor of 1/3R BMD in DM patients, which was compatible with the findings that the patients with primary and secondary hyperparathyroidism had lower BMD predominantly in cortical bone [23]. The previous reports indicated that the diabetic state is an important factor that may reduce bone turnover in dialysis patients through modulation of parathyroid function [22]. Moreover, the present data suggest that secondary hyperparathyroidism is more important for cortical bone in DM patients than in CGN patients.

BMI was positively correlated with UDR-BMD and a positive predictor for UDR-BMD in DM patients. It is generally accepted that higher BMI possesses positive impact on BMD, and that serum leptin levels are correlated with radial BMD in HD patients [24, 25]. A previous study indicated that the degree of obesity in patients with higher BMD was significantly severer than that in HD patients with DM with lower BMD [17], supporting the importance of BMI for bone mass in trabecular bone. Obesity offers protection against osteoporosis, perhaps as a result of enhanced conversion of testosterone to estradiol and of androstenedione to estrone in peripheral fat [26] and increased mechanical stress on biomechanical basis [27]. In the present study, although all samples were collected under similar conditions, blood samples were collected just before regular HD (not fasting), thus, the absolute value of triglyceride might not reflect the nutritional state exactly. Therefore, we cannot assess the significance of nutritional state for BMD in HD patients from the present study.

Serum βMG level was significantly higher in DM

patients with HD, compared to those in CGN patients in the present study. Serum βMG was positively correlated with LS- and UDR-BMD in DM patients, and it was a positive predictor for UDR-BMD. Canalis *et al.* [28] reported that βMG exists in bone and exerts anabolic effects on osteoblasts. These findings suggest that βMG plays some role in maintaining bone mass in HD patients with DM. However, βMG is elevated due to the reduction of glomerular filtration rate, and it is also the cause of amyloidosis in HD patients, although it might have a beneficial role in maintaining BMD in trabecular bone. Therefore, the merit of increasing βMG is contradictory.

The present results were compatible with the findings that serum creatinine level is generally lower in HD patients with DM. In the present study, serum level of creatinine was selected as a negative predictor for UDR-BMD in DM patients. In several studies [2, 29], the duration of HD was related to BMD in HD patients, although Stein *et al.* reported that there was no correlation between them [30]. Serum level of creatinine was related to duration of HD and it was positively correlated with duration of HD in the present study ($r = 0.399$, $p = 0.0021$). Since duration of HD was shorter in DM patients, compared to that in CGN patients, duration of HD might not be selected as a predictor of BMD. In place of duration of HD, serum creatinine might affect trabecular BMD in DM patients.

In conclusion, BMD at forearm was comparable between DM and CGN in HD patients. The determinants of BMD seemed to be different between DM and CGN.

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