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Original Article

Inverse relationship of bone mineral density and serum level of N-terminal pro-B-type natriuretic peptide in peritoneal dialysis patients

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ABSTRACT

Objective: Chronic kidney disease is associated with decreased bone mineral density (BMD). In this study, the relationship between BMD and the fasting serum concentration of N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) was evaluated in peritoneal dialysis (PD) patients.
Material and Methods: Fasting blood samples were obtained from 52 PD patients. BMD was measured by dual energy X-ray absorptiometry of the lumbar vertebrae (L2–L4). The serum NT-pro-BNP level was measured by an electrochemiluminescence immunoassay.
Results: Ten patients (19.2%) had osteoporosis, 23 patients (44.2%) had osteopenia, and 19 patients had normal BMD. Increased serum NT-pro-BNP ($p < 0.001$), advanced age ($p = 0.012$), decreased body mass index ($p = 0.006$), body height ($p = 0.018$), and body weight ($p = 0.004$) were associated with lower lumbar T-scores, but sex, menopausal status, PD modality, diabetes mellitus, and hypertension were not. Multivariate forward stepwise linear regression analysis with adjustment for age, body height, body weight, body mass index, and log-NT-pro-BNP indicated that a high serum level of log-NT-pro-BNP (R^2 change = 0.346; $p < 0.001$) and low body weight (R^2 change = 0.208; $p < 0.001$) were significantly and independently associated with poor lumbar BMD.
Conclusion: A high serum level of NT-pro-BNP and low body weight were associated with poor BMD in PD patients.

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1. Introduction

N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) is the inactive amino terminal fragment that is a cleavage product of pro-BNP. It is secreted by the heart along with biologically active BNP, and is one of the natriuretic peptides [1]. Recent studies have shown that elevated serum NT-pro-BNP is an independent predictor of adverse outcomes from congestive heart failure [2]. In hemodialysis patients, elevated serum NT-pro-BNP is associated with hypervolemia and mortality [3,4].

Bone mineral density (BMD), an indication of bone mass and mineralization, is one of the major determinants of bone strength [5]. Several factors can affect bone metabolism, including age, sex, activity of the renin–angiotensin system (RAS), and the levels of adipokines [6,7]. The natriuretic peptides inhibit the RAS and are potent lipolytic agents that act in adipose tissue and influence BMD [8–10]. There is a high prevalence of reduced bone mass or BMD such as osteopenia and osteoporosis in the general population and it is common in patients with chronic kidney disease (CKD) and those on maintenance dialysis [11,12]. Previous research has shown that reduced BMD in hemodialysis patients is associated with an increased prevalence of osteoporosis in the mid-radius (50–80%), femoral neck (16–47%), lumbar spine (13–29%), and the total body

Conflicts of interest: none.

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(~50%) [12]. Another study of peritoneal dialysis (PD) patients reported a prevalence of osteoporosis of 19.5% in the lumbar spine and 26% in the femoral neck based on T-scores [13]. In the presence of osteoporosis or osteopenia, bone mineral loss in PD patients was as high as 56% [13]. Another study reported that lower BMD was associated with worse outcomes in dialysis patients [11].

Our previous study found that the serum concentration of long-acting natriuretic peptide was negatively associated with lumbar BMD in renal transplant recipients [14]. However, no studies have examined the relationship of lumbar BMD with the serum level of NT-pro-BNP in PD patients. The aim of this study was to determine the relationship between the serum NT-pro-BNP concentration and lumbar BMD in PD patients.

2. Materials and methods

2.1. Patients

The Protection of Human Subjects Institutional Review Board of Tzu Chi University and Hospital approved this prospective study (IRB098-63), and all participants provided informed consent. Fifty-two PD patients at Tzu-Chi General Hospital (Hualien, Taiwan) were enrolled in March 2010. This group consisted of 20 men and 32 women (17 of whom were postmenopausal), and the age range was 19–73 years. The exclusion criteria were acute infection, malignancy, acute myocardial infarction, pulmonary edema, heart failure at the time of blood sampling, use of osteoporosis drugs (bisphosphonates, teriparatide, or estrogen medications), or history of lumbar fracture or surgery. The weekly fractional clearance index for urea (weekly Kt/V), total clearance (peritoneal clearance added to residual clearance), and creatinine clearance (Clcr) were obtained from medical record.

2.2. Anthropometric analysis

Body weight was measured to the nearest half kg with the patient in light clothing without shoes. Height was measured to the nearest half centimeter. Body mass index (BMI) was calculated as the weight (kg) divided by height squared (m^2) [14–16].

2.3. Biochemical determinations

Fasting blood samples (approximately 5 mL) were immediately centrifuged at 3000 *g* for 10 minutes after collection. Serum samples were stored at 4°C and used for biochemical analyses within 1 h of collection. Serum levels of creatinine fasting glucose, total cholesterol, triglycerides, high-density lipoprotein-cholesterol, albumin, globulin, total calcium, and phosphorus were measured using an autoanalyzer (COBAS Integra 800, Roche Diagnostics, Basel, Switzerland). Serum samples were assayed for NT-pro-BNP by an electrochemiluminescence immunoassay on the Elecsys 2010 Immunoanalyzer (Roche Diagnostics, Indianapolis, IN, USA) [15,16]. Serum intact parathyroid hormone (iPTH; Diagnostic Systems Laboratories, Webster, Texas, USA) was measured using a commercially available enzyme-linked immunosorbent assay [14].

2.4. BMD measurements

After blood sampling, patients were immediately given BMD measurements. The BMD in the lumbar vertebrate (L2–L4) was measured using dual energy X-ray absorptiometry (QDR 4500, Hologic Inc., Bedford, MA, USA). BMD is expressed as an absolute value (g/cm^2), as a Z-score, and as a T-score (deviation from peak BMD) [14]. The Z-score was defined as the number of standard deviations from the mean BMD of age-, weight-, and ethnicity-matched healthy individuals. The T-score was defined as the number of standard deviations from the mean BMD of sex-matched young control individuals. Compared with the control value, a lumbar bone T-score < -2.5 was used as the diagnostic cut-off for osteoporosis and a lumbar bone T-score of -1.0 to -2.5, was used for a diagnosis of osteopenia, according to World Health Organization criteria [14].

2.5. Statistical analysis

Data were tested for normal distribution using the Kolmogorov–Smirnov test. Data were expressed as means ± standard deviation for normally distributed data and as medians and interquartile ranges for non-normally distributed data. The glucose, iPTH, NT-pro-BNP, total clearance, and Clcr datasets showed skewed non-normal distributions and therefore these were recalculated by transformation to the base 10 logarithm; after this transformation the log-glucose, log-iPTH, log-NT-pro-BNP, log-total clearance, and log-Clcr then became normally distributed. The significance of differences between groups (normal, osteopenia, and osteoporosis) was determined using the Kruskal–Wallis test for parameters that had non-normal distributions and by one-way analysis of variance for normally distributed data. Comparisons between patients were performed using Student independent *t* test (2-tailed) for normally distributed data. Clinical variables that correlated with lumbar BMD in PD patients were evaluated by univariable linear regression analysis. Variables that were significantly associated with lumbar BMD in PD patients were tested for independence by multivariate forward stepwise regression analysis. All statistical analyses employed SPSS for Windows (version 19.0; SPSS Inc., Chicago, IL, USA). A p-value < 0.05 was considered statistically significant.

3. Results

Table 1 shows the anthropometric and biochemical data of all 52 PD patients, and Table 2 shows the age and clinical characteristics of the three bone density groups (normal, osteopenia, and osteoporosis). Ten patients (19.2%) had osteoporosis, 23 patients (44.2%) had osteopenia, and 19 patients (36.5%) had normal BMD. The results show that older age ($p = 0.012$), decreased height ($p = 0.018$), low BMI ($p = 0.006$), low body weight ($p = 0.004$), and elevated serum NT-pro-BNP ($p < 0.001$) were significantly associated with poor BMD (low lumbar T-score).

Table 3 shows the clinical characteristics and lumbar BMD (g/cm^2) of all 52 PD patients. The results show that lumbar BMD was not significantly affected by sex, presence of diabetes mellitus (DM), hypertension, smoking, mode of PD, or menopausal status. Moreover, the NT-pro-BNP values were not significantly associated with sex, presence of DM, hypertension, smoking, menopausal status, or mode of PD (data not shown).

Univariable linear analysis of the lumbar BMD in the 52 PD patients is presented in Table 4. Height ($r = 0.332$, $p = 0.016$), body weight ($r = 0.570$, $p < 0.001$), and BMI ($r = 0.537$, $p < 0.001$) was positively correlated, while age ($r = -0.320$, $p = 0.021$), and log-NT-pro-BNP ($r = -0.589$, $p < 0.001$) were negatively correlated with lumbar BMD in the 52 PD patients.

Table 5 shows the results of a multivariate forward stepwise linear regression analysis of the relationship of age, height, body weight, BMI, and log-NT-pro-BNP with BMD. These results show a significant and independent association of lumbar BMD with the level of log-NT-pro-BNP (R^2 change $= 0.346$, $p < 0.001$) and body weight (R^2 change $= 0.208$, $p < 0.001$).

Table 1
Anthropometric and biochemical data of the 52 peritoneal dialysis patients.

Items	Parameter		Parameter	
Anthropometric data	Height (cm)	159.32 ± 8.51	Age (y)	52.85 ± 13.16
	Body weight (kg)	62.30 ± 13.86	PD duration (mo)	41.79 ± 37.35
	Body mass index (kg/m^2)	24.37 ± 4.15	SBP (mmHg)	134.04 ± 24.00
	DBP (mmHg)	77.25 ± 15.85	Lumbar T-score	−1.42 ± 1.30
	Lumbar T-score	−0.90 ± 0.84	Lumbar BMD (g/cm^2)	0.66 ± 0.15
Biochemical data	Albumin (g/dL)	3.83 ± 0.44	Globulin (g/dL)	2.94 ± 0.54
	Triglyceride (mg/dL)	209.06 ± 134.13	Total cholesterol (mg/dL)	194.60 ± 51.62
	HDL-C (mg/dL)	43.96 ± 13.73	Creatinine (mg/dL)	10.24 ± 3.03
	Fasting glucose (mg/dL)	94.50 (86.00–110.00)	Total Calcium (mg/dL)	9.66 ± 0.66
	Phosphorus (mg/dL)	5.27 ± 1.20	Ca × P product (mg^2/dL^2)	50.92 ± 11.96
	iPTH (pg/mL)	291.7 (157.53–605.18)	NT-pro-BNP (pg/mL)	2035.50 (1223.00–5303.25)
	Weekly Kt/V	2.03 ± 0.40	Total clearance (L/week)	54.28 (48.51–70.23)
	Clcr (mL/min)	0.94 (0.00–3.38)		

Values for continuous variables given as means ± standard deviation; variables not normally distributed given as medians and interquartile range.
BMD = bone mineral density; Clcr = creatinine clearance; DBP = diastolic blood pressure; HDL-C = high density lipoprotein cholesterol; iPTH = intact parathyroid hormone; Kt/V = fractional clearance index for urea; NT-pro-BNP = N-terminal pro-B-type natriuretic peptide; PD = peritoneal dialysis; SBP = systolic blood pressure.

Table 2
Clinical characteristics of the 52 peritoneal dialysis patients with different lumbar T-scores.

Characteristic	Normal (n = 19) T-score > −1	Osteopenia (n = 23) −2.5 < T-score ≤ −1	Osteoporosis (n = 10) T-score ≤ −2.5	p
Age (y) [a]	47.47 ± 12.81	53.13 ± 13.09	62.40 ± 8.46	0.012*
Peritoneal dialysis duration (mo) [a]	47.00 ± 37.46	37.78 ± 34.55	41.10 ± 45.62	0.735
Height (cm) [a]	160.16 ± 8.65	161.50 ± 7.22	152.70 ± 8.42	0.018*
Body weight (kg) [a]	68.46 ± 14.14	62.08 ± 12.95	51.11 ± 7.69	0.004*
Body mass index (BMI; kg/m^2) [a]	26.54 ± 4.29	23.68 ± 3.93	21.85 ± 2.17	0.006*
Lumbar T-score [a]	−0.10 ± 0.95	−1.77 ± 0.42	−3.12 ± 0.39	< 0.001*
Lumbar Z-score [a]	−0.08 ± 0.84	−1.05 ± 0.47	−1.93 ± 0.59	< 0.001*
Lumbar bone density mass (g/cm^2) [a]	0.79 ± 0.12	0.64 ± 0.07	0.46 ± 0.05	< 0.001*
Albumin (g/dL) [a]	4.01 ± 0.38	3.76 ± 0.40	3.68 ± 0.58	0.095
Globulin (g/dL) [a]	2.88 ± 0.61	2.97 ± 0.53	3.00 ± 0.47	0.829
Total cholesterol (mg/dL) [a]	208.89 ± 64.01	189.43 ± 35.68	179.30 ± 55.09	0.282
Triglyceride (mg/dL) [a]	255.05 ± 160.02	176.04 ± 122.74	197.60 ± 80.68	0.158
High density lipoprotein (HDL; mg/dL) [a]	42.73 ± 15.06	42.74 ± 10.41	49.10 ± 17.70	0.428
Fasting glucose (mg/dL) [b]	117.00 (95.00–179.00)	104.00 (91.00–159.00)	115.50 (104.00–256.25)	0.303
Creatinine (mg/dL) [a]	10.92 ± 3.63	10.38 ± 2.74	8.63 ± 1.78	0.146
Total calcium (mg/dL) [a]	9.51 ± 0.73	9.73 ± 0.62	9.76 ± 0.63	0.509
Phosphorus (mg/dL) [a]	5.57 ± 0.95	5.32 ± 1.15	4.62 ± 1.60	0.125
Ca × P product (mg^2/dL^2) [a]	53.02 ± 10.08	15.92 ± 12.24	44.63 ± 13.63	0.174
Intact parathyroid hormone (pg/mL) [b]	220.20 (142.40–527.30)	375.80 (184.40–815.10)	271.10 (124.50–396.98)	0.199
NT-pro-BNP (pg/mL) [b]	1223.00 (879.00–1794.00)	2772.00 (1780.00–4216.00)	5733.00 (5367.00–6179.00)	< 0.001*
Systolic blood pressure (mmHg) [a]	137.79 ± 26.14	135.61 ± 20.83	123.30 ± 25.92	0.282
Diastolic blood pressure (mmHg) [a]	77.21 ± 17.90	80.65 ± 16.46	69.50 ± 9.66	0.180
Weekly Kt/V [a]	2.06 ± 0.42	2.07 ± 0.43	1.88 ± 0.27	0.428
Total clearance (L/week)	62.27 (46.98–77.45)	52.95 (50.36–78.99)	54.19 (42.28–61.53)	0.327
Clcr (mL/min)	0.9 (0.00–5.09)	0.97 (0.00–3.09)	1.00 (0.00–2.77)	0.881

BMD = bone mineral density; Clcr = creatinine clearance; HDL-C = high-density lipoprotein-cholesterol; Kt/V = fractional clearance index for urea; LDL-C = low-density lipoprotein-cholesterol; NT-pro-BNP = N-terminal pro-B-type natriuretic peptide.
[a] Data tested by one-way analysis of variance.
[b] Data tested by Kruskal–Wallis analysis; * $p < 0.05$ was considered statistically significant after Kruskal–Wallis analysis or one-way analysis of variance (ANOVA).

Table 3
Clinical characteristics and lumbar bone mineral density levels of the 52 peritoneal dialysis patients.

Characteristic		Number (%)	Lumbar BMD (g/cm^2)	p
Sex	Male	20 (38.5)	0.68 ± 0.17	0.394
	Female	32 (61.5)	0.64 ± 0.14	
DM	No	32 (61.5)	0.65 ± 0.13	0.563
	Yes	20 (38.5)	0.67 ± 0.18	
Hypertension	No	21 (40.3)	0.67 ± 0.14	0.741
	Yes	31 (59.7)	0.65 ± 0.15	
PD model	CAPD	43 (82.7)	0.66 ± 0.14	0.975
	APD	9 (17.3)	0.66 ± 0.19	
Smoking	No	42 (80.7)	0.65 ± 0.15	0.262
	Yes	10 (19.3)	0.71 ± 0.13	
Menopause	No	15 (47.9)	0.69 ± 0.13	0.081
	Yes	17 (51.1)	0.60 ± 0.13	

*$p < 0.05$ was considered statistically significant after the Student's independent t test.
APD = ambulatory peritoneal dialysis; CAPD = continuous ambulatory peritoneal dialysis; DM = diabetes mellitus; PD = peritoneal dialysis.

4. Discussion

The major results of this study of 52 PD patients are that body weight had a significant and independent positive association with lumbar BMD, and that the fasting serum level of NT-pro-BNP had a significant and independent negative association with lumbar BMD. In addition, analysis of the three defined bone density groups (normal, osteopenia, and osteoporosis) indicated that an increased serum NT-pro-BNP level was significantly correlated with a low lumbar T-score.

Disorders of bone metabolism are common in patients with CKD, and bone strength declines more severely as CKD progresses than during the normal aging process [5,17]. Abnormal bone strength can cause musculoskeletal pain, negatively impact quality of life, and increase the risk for bone fracture [17]. A study of PD patients in Poland indicated that many patients had osteoporosis (15.4%) and osteopenia (38.5%) in the femoral neck [17]. Similarly, a study of PD patients in Korea indicated that osteoporosis of the

Table 4
Correlation of lumbar bone mineral density levels and clinical variables by univariate linear regression analysis among the 52 peritoneal dialysis patients.

Variable	R value	*p*
Age	−0.320	0.021*
Peritoneal dialysis duration	−0.017	0.906
Height	0.332	0.016*
Body weight	0.570	< 0.001*
Body mass index	0.537	< 0.001*
Albumin	0.265	0.058
Globulin	−0.093	0.513
Total cholesterol	0.096	0.497
Triglyceride	0.132	0.352
High density lipoprotein	−0.244	0.081
Log-glucose	−0.060	0.672
Creatinine	0.257	0.065
Total calcium	−0.127	0.368
Phosphorus	0.254	0.069
Ca × P product	0.217	0.123
Log-intact parathyroid hormone	0.022	0.877
Log-NT-pro-BNP	−0.589	< 0.001*
Systolic blood pressure	0.223	0.112
Diastolic blood pressure	0.120	0.398
Weekly Kt/V	0.095	0.504
Log-total clearance	0.260	0.062
Log-Clcr	0.190	0.289

Data of glucose, iPTH, NT-pro-BNP, total clearance, and Clcr levels showed skewed distribution, and therefore were log-transformed before analysis; *$p < 0.05$ is considered statistically significant in the univariate linear analyses.
Clcr = creatinine clearance; Kt/V = fractional clearance index for urea; NT-pro-BNP = N-terminal pro-B-type natriuretic peptide.

femoral neck (7%) and the lumbar spine (17%) and osteopenia of the femoral neck (53%) and lumbar spine (41%) were common [18]. Our previous study also indicated that lumbar spine osteoporosis (11.6%) and osteopenia (40.6%) were common in renal transplant recipients [14]. In the present study, 19.2% of Taiwanese PD patients had osteoporosis and 44.2% had osteopenia of the lumbar spine.

Traditional risk factors, such as advanced age, female sex, hormonal factors, decreased physical activity, thin body habitus, cigarette smoking, alcohol abuse, and possibly some genetic factors increase the risk for osteoporosis [12]. In addition to these traditional risk factors for low BMD, patients with CKD have additional risk factors, including hyperparathyroidism, 1,25-dihydroxyvitamin D deficiency, use of immunosuppression therapy, chronic metabolic acidosis, secondary amenorrhea, and heparin exposure (in dialyzed patients) [19,20]. In the present study, we found no significant effect of sex, smoking, menopause, DM, hypertension, or modality of PD on BMD in PD patients. Univariate analysis indicated that advanced age was associated with BMD, but this factor was not significantly associated with BMD in multivariate analysis.

Low BMI is a known risk factor for osteoporosis [21], and loss of BMD is a common complication that correlates with low body weight and low BMI in renal transplantation recipients [22]. Our previous study of renal transplant recipients indicated that body height, body weight, and BMI were positively correlated with lumbar BMD [14]. In addition, Atsumi et al indicated an inverse relationship between body weight and osteoporosis in patients undergoing hemodialysis [23], and Jeong el al reported that nutritional markers such as age, BMI, albumin, and prealbumin were independent predictors of femoral neck T-scores and BMI as a predictor of L-spine T-scores [18]. Ersoy et al [13] studied 292 PD patients and found that BMI was strongly correlated with BMD. They postulated that the factor most responsible for this strong statistical correlation was patient weight rather than height [13]. Similarly, our multivariate analysis indicated that body weight was positively correlated with BMD in PD patients.

Table 5
Multivariate stepwise linear regression analysis of the association of age, height, body weight, body mass index, and log-NT-pro-BNP with lumbar bone mineral density in 52 peritoneal dialysis patients.

Items	β	R^2	R^2 change	Adjusted R^2	*p*
Log-NT-pro-BNP	−0.490	0.346	0.346	0.333	< 0.001*
Body weight	0.467	0.554	0.208	0.203	< 0.001*

*$p < 0.05$ is considered statistically significant in the multivariate stepwise linear regression analysis.
NT-pro-BNP = N-terminal pro-B-type natriuretic peptide.

A previous study of dialysis patients reported that NT-pro-BNP was associated with increased left ventricular mass and ejection fraction, and was a better predictor of 3-month to 5-year mortality than high sensitivity C-reactive protein or cardiac troponin T [24]. However, few studies have examined the association of NT-pro-BNP with BMD in dialysis patients. A study of transgenic mice indicated that activation of the RAS induced osteoporosis independently of hypertension [25], and a study of a hypertensive rat model indicated that inhibitors of the RAS attenuated osteoporosis [26]. Clinical studies also reported that administration of angiotensin-converting enzyme inhibitors increased BMD [27,28]. Natriuretic peptide inhibits the RAS axis by binding its common receptor, guanylyl cyclase-A, which leads to activation through a cyclic guanosine monophosphate (cGMP)-dependent pathway [10]. In addition, natriuretic peptides are potent lipolytic agents that act in adipose tissue via the BNP—cGMP-dependent protein kinase cascade, which increases fat oxidation [8,29]. Body weight is a function of fat mass and lean mass, and could impact bone turnover and bone density [30,31]. Thus, the pathophysiological relevance of natriuretic peptide in bone integrity may be explained by the participation of adipokines in bone remodeling due to their effects on bone deposition and resorption [31]. We previously found that NT-pro-BNP levels were significantly correlated with poor lumbar T-scores and proposed that NT-pro-BNP plays a role in the regulation of BMD [14]. In other words, there is a negative association between natriuretic peptides and BMD in renal transplant recipients [14]. In the present study, we also found that increased serum NT-pro-BNP levels were associated with poor lumbar T-scores and the serum level of NT-pro-BNP was a significant and independent predictor of lumbar BMD in PD patients.

The present study had some limitations. First, only a small number of PD patients were enrolled, so the statistical power for comparison of groups was weak. Second, this study had a cross-sectional design, and did not employ a control group. Therefore, the findings of this study must be confirmed by long-term prospective studies before a causal relationship between serum NT-pro-BNP and BMD in PD patients can be established.

In conclusion, this study of PD patients from Taiwan indicated that the fasting serum NT-pro-BNP level was negatively associated and that body weight was positively associated with lumbar BMD.

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