

Original

Characteristics of Bone Mineral Density and Tartrate-resistant Acid Phosphatase (TRACP) 5b in Patients Receiving Hemodialysis Therapy for More-than-30-years

Shigeru OTSUBO^{1,2}, Yasuko YABUKI¹, Miwa ISHIHARA¹, Naoki KIMATA³,
Keiko UCHIDA⁴, Takashi AKIBA³ and Kosaku NITTA⁴

¹Department of Blood Purification, Sangenjaya Hospital

²Department of Nursing, Faculty of Human Care, Tohto College of Health Sciences

³Department of Blood Purification, Kidney Center, Tokyo Women's Medical University

⁴Department of Medicine IV, Tokyo Women's Medical University School of Medicine

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Objective: Chronic kidney disease-mineral and bone disorder (CKD-MBD) is a regular complication of hemodialysis patients. On the other hand, with advances in strategies for hemodialysis therapy, the number of extremely long-term survivors of CKD receiving hemodialysis has been increasing. We investigated tartrate-resistant acid phosphatase (TRACP) 5b which is reportedly not affected by renal function, and the bone mineral density (BMD), of extremely long-term hemodialysis patients. **Methods:** Ninety-three outpatients receiving maintenance hemodialysis (including 18 for more-than-30-years) at the Sangenjaya Hospital were enrolled. The serum levels of TRACP-5b were measured before the start of the hemodialysis session. BMD was assessed using dual-energy X-ray absorptiometry scans. We classified the patients according to the duration of hemodialysis therapy (less-than-10-years (n = 57), 10-20-years (n = 10), 20-30-years (n = 8), or more-than-30-years (n = 18)) and compared the TRACP-5b and BMD among the groups. **Results:** The TRACP-5b level was higher in the more-than-30-years group, compared with each of the other groups (p < 0.0001). The BMD and Z score was 0.59 ± 0.17 g/cm² and -0.26 ± 1.42 in less-than-10-years group, 0.59 ± 0.16 g/cm² and -1.50 ± 2.33 in 10-20-years group, 0.45 ± 0.12 g/cm² and -2.23 ± 1.16 in 20-30-years group and 0.43 ± 0.13 g/cm² and -3.21 ± 1.86 in more-than-30-years group. The BMD was lower in the more-than-30-years group than in the less-than-10-years (p = 0.019) and 10-20-years (p = 0.013) groups. The Z score was reduced gradually according to the duration of hemodialysis and was significantly lower in the more-than-30-years group than in the less-than-10-years (p < 0.0001) and 10-20-years (p = 0.009) groups. BMD was negatively correlated with the serum level of TRACP-5b (p < 0.0001). **Conclusion:** The serum TRACP-5b level is closely related to the BMD. In extremely long-term hemodialysis outpatients (for more-than-30-years), the BMD was reduced while the serum TRACP-5b level was relatively high.

Key Words: bone mineral density, bone markers, long-term hemodialysis, tartrate-resistant acid phosphatase 5b

Introduction

Chronic kidney disease-mineral and bone disorder (CKD-MBD) is a regular complication of hemodialysis patients¹⁾ and leads to substantial increases in the fracture rate, morbidity, and mortality²⁾. Bone mineral density (BMD) and biochemical parameters are widely applied for the assessment of renal os-

teodystrophy. Cortical BMD was reported to be a predictor of prevalent fractures in hemodialysis patients³⁾. The measurement of serum tartrate-resistant acid phosphatase (TRACP) 5b has been reported to be independent of renal dysfunction and to be a clinically relevant assay for estimating the bone metabolic status of hemodialysis patients^{4,5)}.

Table 1 Background characteristics of outpatients receiving maintenance hemodialysis

Parameters	
Number (male/female)	93 (62/31)
Age (years)	67.2 ± 12.3
HD duration (years)	11.8 ± 12.7
Cause of ESKD n (%)	
Chronic glomerulonephritis	41 (44.1)
Diabetic nephropathy	26 (28.0)
Nephrosclerosis	13 (14.0)
Others	5 (5.4)
Unknown	8 (8.6)

Values are expressed as mean ± SD.

HD: hemodialysis, ESKD: end-stage kidney disease.

On the other hand, with advances in strategies for hemodialysis therapy, the number of long-term survivors of CKD receiving hemodialysis has been increasing. Because there are not enough renal transplantation donors in Japan, the duration of hemodialysis therapy is much longer than in other countries⁶. Therefore, Japan provides an ideal setting for describing patients receiving extremely long-term dialysis. Little information is presently available concerning CKD-MBD in patients receiving extremely long-term hemodialysis. In the present study, we investigated several biochemical parameters, including TRACP-5b and the BMD, of extremely long-term hemodialysis patients.

Patients and Methods

Of all outpatients receiving maintenance hemodialysis, 93 patients (including 18 for more-than-30-years) who agree to examine were enrolled. Clinical data were collected, including age, sex, duration of hemodialysis therapy, cause of end-stage kidney disease (ESKD), and medical history of operation for dialysis-related amyloidosis.

We classified the patients according to the duration of hemodialysis therapy (less-than-10-years, 10-20-years, 20-30-years, or more-than-30-years) and compared the laboratory data and BMD among the groups.

The serum levels of albumin, calcium, phosphorous, alkaline phosphatase (ALP), intact parathyroid hormone (i-PTH) and TRACP-5b were measured before the start of the hemodialysis session. TRACP-5b, which is reportedly not affected by re-

nal function, was measured using a novel fragments-absorbed immunocapture enzymatic assay (FAICEA) and two monoclonal antibodies⁷. Routine chemistry profiles were determined using standard methods. The calcium concentration was corrected according to the albumin concentration using the following formula⁸: corrected Ca (mg/dL) = measured serum Ca (mg/dL) + 0.8 × [4-serum albumin (g/dL)].

Bone mineral density (BMD) was assessed using dual-energy X-ray absorptiometry (DEXA) scans. The absolute BMD values for the 1/3 distal radius on the side not containing the vascular access were reported.

All the data were expressed as the means ± S.D. The Student's t-test was used for comparisons between continuous variables. A simple regression analysis was used to examine the relationship between two continuous variables. All statistical calculations were performed using Stat View SE. P values less than 0.05 were considered to denote statistical significance. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Results

Background characteristics of outpatients receiving maintenance hemodialysis

The patient characteristics are shown in Table 1. The mean age was 67.2 ± 12.3 years, and the mean duration of hemodialysis was 11.8 ± 12.7 years. The most prevalent cause of ESKD was chronic glomerulonephritis (44.1%).

Comparison of laboratory data and BMD among patients according to the duration of hemodialysis

The patient characteristics, including age and laboratory data, and the BMD of the 4 groups divided according to the duration of hemodialysis therapy are shown in Table 2. No significant differences in age were observed among the 4 groups. The TRACP-5b level was 1,192.4 ± 484.1 mU/dL, and the BMD was 0.43 ± 0.13 g/cm² in the more-than-30-years group. The TRACP-5b level was higher in the more-than-30-years group, compared with each of the other groups (p < 0.0001). The BMD

Table 2 Comparison of laboratory and anthropometric data among patients according to the duration of hemodialysis

	Duration of hemodialysis (years)			
	<10	10-20	20-30	30<
Number (M/F)	57 (38/19)	10 (8/2)	8 (4/4)	18 (12/6)
Age (years)	68.6 ± 13.9	64.1 ± 12.6	67.4 ± 8.5	64.5 ± 6.7
Duration of HD (years)	3.0 ± 2.6	13.4 ± 3.0	23.1 ± 2.0	33.9 ± 2.5
Corrected Ca (mg/dl)*	9.3 ± 0.6	9.4 ± 0.6	9.8 ± 0.3	9.6 ± 0.5
Phosphorous (mg/dl)	5.3 ± 1.4	5.5 ± 0.7	5.2 ± 1.2	5.0 ± 1.0
Ca-P (mg ² /dl ²)	49.2 ± 12.6	52.1 ± 8.8	51.2 ± 11.7	45.4 ± 15.0
ALP (IU/l)**	278.6 ± 150.2	191.9 ± 48.1**	243.5 ± 93.8	343.1 ± 175.0
i-PTH (pg/ml)	195.9 ± 156.3	180.4 ± 117.4	205.4 ± 192.6	185.1 ± 131.4
TRACP-5b (mU/dl)***	479.6 ± 253.3	456.7 ± 296.4	509.6 ± 256.3	1,192.4 ± 484.1
BMD (g/cm ²)#	0.59 ± 0.17	0.59 ± 0.16	0.45 ± 0.12	0.43 ± 0.13
Z score##	-0.26 ± 1.42	-1.50 ± 2.33	-2.23 ± 1.16	-3.21 ± 1.86
Operation for CTS n (%)	1 (1.8)	0 (0)	5 (62.5)	17 (94.4)
Operation for cervical DSA n (%)	0 (0)	0 (0)	0 (0)	6 (33.3)
Cause of ESKD n (%)				
Chronic glomerulonephritis	8 (14.0)	7 (70.0)	8 (100.0)	18 (100.0)
Diabetic nephropathy	24 (42.1)	2 (20.0)	0 (0.0)	0 (0.0)
Nephrosclerosis	13 (22.8)	0 (0.0)	0 (0.0)	0 (0.0)
Others	4 (7.0)	1 (10.0)	0 (0.0)	0 (0.0)
Unknown	8 (14.0)	0 (0.0)	0 (0.0)	0 (0.0)

Values are expressed as mean ± SD.

*: $p = 0.0267$ (<10 vs 20-30), $p = 0.0386$ (<10 vs 30<).

** : $p = 0.096$ (10-20 vs 30<).

***: $p < 0.0001$ (30< vs each other groups).

: $p = 0.0189$ (<10 vs 20-30), $p = 0.0003$ (<10 vs 30<), $p = 0.0157$ (10-20 vs 30<).

##: $p = 0.0275$ (<10 vs 10-20), $p = 0.0171$ (<10 vs 20-30), $p < 0.0001$ (<10 vs 30<), $p = 0.0085$ (10-20 vs 30<).

HD: hemodialysis, Ca: calcium, P: phosphorous, ALP: alkaline phosphatase, i-PTH: intact parathyroid hormone, TRACP: tartrate-resistant acid phosphatase, BMD: bone mineral density, CTS: carpal tunnel syndrome, DSA: destructive spondyloarthropathy.

Table 3 Correlations of bone mineral density with mineral bone disease-related parameters

	Bone mineral density	
	r	P
Age (years)	-0.361	0.0004
HD duration (years)	-0.381	0.0002
Corrected Ca (mg/dl)	-0.146	NS
Phosphorous (mg/dl)	0.068	NS
Ca × P (mg ² /dl ²)	0.062	NS
ALP (IU/l)	-0.180	NS
i-PTH (pg/ml)	0.022	NS
TRACP-5b (mU/dl)	-0.426	<0.0001

HD: hemodialysis, Ca: calcium, P: phosphorous, ALP: alkaline phosphatase, i-PTH: intact parathyroid hormone, TRACP: tartrate-resistant acid phosphatase.

was lower in the more-than-30-years group than in the less-than-10-years ($p = 0.0189$) and 10-20-years ($p = 0.0126$) groups. The Z score was reduced gradually according to the duration of hemodialysis and

was significantly lower in the more-than-30-years group than in the less-than-10-years ($p < 0.0001$) and 10-20-years ($p = 0.0085$) groups. Almost of all patients underwent operation for carpal tunnel syndrome (17 out of 18, 94.4%), and 6 out of 18 (33.3%) underwent operation for cervical destructive spondyloarthropathy in more-than-30-years group. The cause of ESKD was chronic glomerulonephritis in all patients with more-than-20-years hemodialysis therapy.

Correlations of BMD with mineral bone disease (MBD)-related parameters

As shown in Table 3, a simple linear regression showed that the BMD was negatively correlated with age ($p = 0.0004$), duration of hemodialysis therapy ($p = 0.0002$) and the serum level of TRACP-5b ($p < 0.0001$, also shown in Figure).

Discussion

We investigated the BMD and several biochemi-

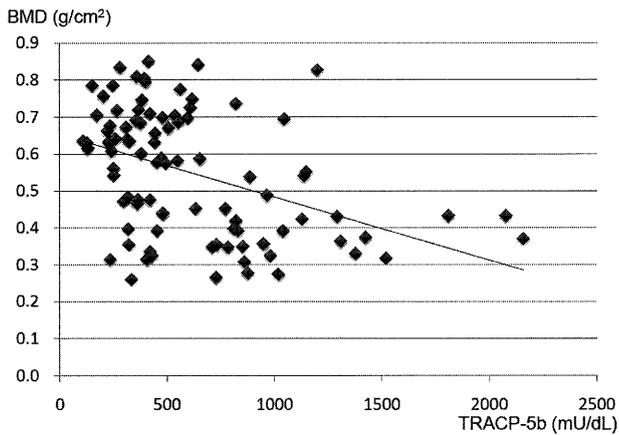


Figure Relation between the bone mineral density (BMD) and the serum tartrate-resistant acid phosphatase (TRACP) 5b level. A negative linear relationship was observed between the two parameters ($r = -0.426$, $p < 0.0001$).

cal parameters including the serum TRACP-5b level. Even though patient age did not differ significantly among the 4 groups when divided according to the duration of hemodialysis, the BMD was significantly lower in the more-than-30-years group than in the other groups, and the serum level of TRACP-5b was significantly higher in the more-than-30-years group than in the other groups. The BMD was negatively and the serum level of TRACP-5b was positively correlated with the duration of hemodialysis. Thus, long-term hemodialysis therapy may affect the bone metabolic status.

Today's ESKD patients are prone to developing accelerated osteoporosis as a result of their increasing age, hormonal status, and multiple comorbidities that limit their physical activity level⁽⁹⁾⁽¹⁰⁾. Physical exercise is advised to prevent reductions in the BMD⁽¹¹⁾. Dialysis-related amyloidosis is one common complication of long-term hemodialysis⁽¹²⁾ that can affect activities of daily living. This complication may limit their physical activity level, resulting in a loss of BMD in extremely long-term hemodialysis patients. Prevention of dialysis-related amyloidosis (such as use of β 2-microglobulin adsorption column or hemodiafiltration) and keep physical exercise may be advised to prevent reductions in the BMD. Dialysis-related amyloidosis causes bone absorption and may affect loss of BMD directly. But we could

not investigate the relation between BMD and β 2-microglobulin because of lack of data.

Biochemical parameters and the BMD are widely applied for the assessment of renal osteodystrophy⁽¹³⁾. The serum PTH level is often measured in routine clinical practice for the noninvasive assessment of the bone metabolic state, but serum bone metabolic markers are superior to serum PTH for this purpose because of the wide individual variation in the PTH responsiveness of bone tissue^{(14)–(16)}. Recent study showed low PTH levels (i-PTH < 100 pg/ml) were not associated low BMD in patients with ESKD⁽¹⁷⁾. Bone resorption markers are assumed to be superior to bone formation markers for predicting the rate of bone loss⁽¹⁸⁾, since most causes of osteoporosis arise from an increase in bone turnover and bone resorption⁽¹⁹⁾⁽²⁰⁾. TRACP-5b is secreted into the circulation by osteoclasts during bone resorption⁽²¹⁾⁽²²⁾ and has been proposed as a marker of bone resorption^{(23)–(26)}. In this study, we also confirmed a remarkable correlation between the BMD and the serum TRACP-5b level. The measurement of serum TRACP-5b levels may be capable of predicting the severity of reductions in BMD.

There are some limitations in this study. The cause of ESKD was not evenly distributed in this study. All of the cause of ESKD in more-than-20-years hemodialysis therapy was chronic glomerulonephritis. High prevalence of chronic glomerulonephritis in relatively long-term hemodialysis patients may affect BMD. We also could not investigate gender influence cause of small subjects.

Conclusion

The serum TRACP-5b level is closely related to the BMD. In extremely long-term hemodialysis outpatients (for more-than-30-years), the BMD was reduced while the serum TRACP-5b level was relatively high.

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透析歴 30 年以上の血液透析患者における骨密度と tartrate-resistant acid phosphatase (TRACP) 5b の特徴

¹三軒茶屋病院血液浄化療法科

²東都医療大学ヒューマンケア学部看護学科

³東京女子医科大学血液浄化療法科

⁴東京女子医科大学医学部内科学 (第四) (主任: 新田孝作教授)

オオツボ	シゲル	ヤブキ	ヤスコ	イシハラ	ミワ	キマタ	ナオキ
大坪	茂 ^{1,2}	矢吹	恭子 ¹	石原	美和 ¹	木全	直樹 ³
ウチダ	ケイコ	アキバ	タカシ	ニツタ	コウサク		
内田	啓子 ⁴	秋葉	隆 ³	新田	孝作 ⁴		

〔目的〕慢性腎臓病に伴う骨ミネラル代謝異常(Chronic kidney disease-mineral and bone disorder, CKD-MBD)は血液透析患者に必発する重要な合併症である。一方、透析技術の進歩に伴い、長期に生存する透析患者が増加してきている。しかし、透析歴 30 年以上の透析患者の骨密度に関する論文報告はない。そこで今回、透析歴 30 年以上の長期透析患者において、骨吸収マーカーである tartrate-resistant acid phosphatase (TRACP) 5b と骨密度を検討した。〔方法〕三軒茶屋病院において維持血液透析を施行している透析歴 30 年以上の患者 18 名を含む 93 名を対象とした。透析前の血清 TRACP-5b を fragments-absorbed immunocapture enzymatic assay (FAICEA) と 2 種類のモノクローナル抗体を使用して測定した。骨密度は非シャント側橈骨遠位 1/3 部にて Dual Energy X-ray Absorptiometry 法で測定した。透析患者を透析歴 (10 年以下 (n=57), 10~20 年 (n=10), 20~30 年 (n=8), 30 年以上 (n=18)) によって 4 群に分け、各群間で TRACP-5b と骨密度を比較した。〔結果〕透析歴 30 年以上の患者において、血清 TRACP-5b 値は $1,192.4 \pm 484.1$ mU/dL で骨密度は 0.43 ± 0.13 g/cm² であった。血清 TRACP-5b 値は透析歴 30 年以上の群において他のそれぞれの群より有意に高値であった ($p < 0.0001$)。骨密度と Z スコアは透析歴 10 年以下の群で 0.59 ± 0.17 g/cm² と -0.26 ± 1.42 , 透析歴 10~20 年の群で 0.59 ± 0.16 g/cm² と -1.50 ± 2.33 , 透析歴 20~30 年の群で 0.45 ± 0.12 g/cm² と -2.23 ± 1.16 , 透析歴 30 年以上の群で 0.43 ± 0.13 g/cm² と -3.21 ± 1.86 であった。骨密度は透析歴 20 年以上で低値で、特に 30 年以上の群において、10 年以下の群および 10~20 年の群より有意に低値であった (それぞれ $p = 0.019$, $p = 0.013$)。骨密度の Z スコアは透析歴に応じて徐々に低下し、透析歴 30 年以上の群において、10 年以下の群および 10~20 年の群と比較し、有意に低値であった (それぞれ $p < 0.0001$, $p = 0.009$)。骨密度は TRACP-5b と強い負の相関を示した ($p < 0.0001$)。〔結論〕TRACP-5b は骨密度と強い負の相関を示した。透析歴 30 年以上の超長期透析患者において骨密度は低値で TRACP-5b は高値であった。