ORIGINAL ARTICLE

Mineral Bone Disorder

Effect of long-term use of unfractionated or low-molecular-weight heparin on bone mineral density in maintenance hemodialysis patients

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ABSTRACT

Introduction: Long-term use of unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) causes bone loss and osteoporosis in patients not receiving hemodialysis. This study aimed to investigate the effect of UFH and LMWH on bone mineral density (BMD) in patients undergoing maintenance hemodialysis (MHD).

Methods: Patients undergoing MHD using UFH or LMWH as anticoagulants were enrolled. BMD (in g/cm^2), T-score and Z-score (BMDs) were measured at the lumbar spine and femur neck using dual-energy X-ray absorptiometry (DXA) at baseline and 2 years later. Patient demographics and clinical indices were collected. Correlation analysis was used to identify significant predictors of bone loss. Multiple linear regression was used to explore the relationship between heparin type and bone loss progression.

Findings: A total of 104 patients were enrolled and completed the baseline BMD test; 72 completed the test again 2 years later. Six patients were excluded because they used both UFH and LMWH. Although BMD decreased in some patients in the UFH group, a slight increase in the BMD was observed on an average in the LMWH group after 2 years. The mean change in BMD (in g/cm^2) [0(−0.03,0.04) vs. 0.04(0,0.06), $P = 0.023$], T-score [0(−0.40,0.30) vs. 0.35(−0.03,0.53), $P = 0.038$], and Z-score [0.10(−0.30,0.40) vs. 0.45(0.08,0.63), $P = 0.031$] in the lumbar spine in the UFH group was lower than those in the LMWH group. Femur neck BMD did not change significantly. In a linear regression model, after adjusting for diabetes mellitus, parathyroid hormone, and serum phosphate, we did not find an association between heparin substances and BMD.

Discussion: UFH might be associated with loss of lumbar spine BMD in patients undergoing MHD.

Keywords: Hemodialysis, heparin, low-molecular-weight heparin, bone mineral density, osteoporosis

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INTRODUCTION

Chronic kidney disease mineral and bone disorder (CKD-MBD) is one of the crucial complications of chronic kidney disease (CKD). In 2009, Kidney Disease: Improving Global Outcomes (KDIGO) guideline made the definition of CKD-MBD, including abnormalities in bone turnover, mineralization, and volume.[1] Low bone mass is frequent especially in patients on dialysis.[2] Osteoporosis characterized by low bone mass is part of renal osteodystrophy and a risk for bone fractures.[3, 4] Particularly, compared to patients without kidney disease, patients with CKD-MBD have a frequency of vertebral and hip fractures up to fourfold greater.[5, 6] Furthermore, osteoporosis-induced bone fractures are associated with reduced quality of life and increased mortality.[7, 8]

Bone mineral density (BMD), measured by dual-energy X-ray absorptiometry (DXA), is a valid method to assess the risk of bone fractures in patients without kidney disease.[9] In the previous guidelines, KDIGO recommended that in patients with CKD G3a-G5D with evidence of CKD-MBD and/or risk factors of osteoporosis, BMD testing should be used to assess the risk of fracture, if the results impact treatment decisions.[10] Yenchek et al. have demonstrated that lower BMD is a risk for fracture in older individuals with or without moderate CKD.[11] In addition, growing evidence shows that BMD can predict fractures in patients on dialysis,[12] although some reports reached the opposite conclusion.[13, 14]

Heparin is an anticoagulant commonly used in clinical practice, especially in hemodialysis treatment. Unfractionated heparin (UFH) is a mucopolysaccharide molecule that exerts anticoagulant effect by binding to antithrombin. Low-molecular-weight heparin (LMWH) is prepared by chemical or enzymatic reactions to reduce the length of the unfractionated heparin pentasaccharide chain. LMWH exerts anticoagulant effect by inhibiting Xa activity by binding to antithrombin.[15] In recent years, animal experiments and clinical observations have confirmed that long-term use of UFH could induce bone loss, osteoporosis, and increase the risk of fracture.[16–18] In vitro, Li et al. found that UFH promoted osteoclastogenesis by inhibiting the activity of osteoprotegerin.[19] The side effects of LMWH were fewer than that of UFH, but the long-term use of LMWH is not without risks.[16]

In patients undergoing MHD, CKD-MBD makes the relationship between heparin and osteoporosis more complex. To date, few studies have focused on the effects of long-term use of UFH or LMWH on BMD change in patients undergoing MHD. According to the criteria for the diagnosis of osteoporosis, lumbar spine and femoral neck are the most common skeletal measured sites.[19] In our prospective cohort of patients undergoing MHD, the relationship between type of heparin and BMD changes in the lumbar spine and femoral neck were analyzed.

MATERIALS AND METHODS

Study design and patients

This single-center prospective, prevalent cohort study was conducted among patients undergoing MHD. This study was approved by the Ethics Committee of Peking University People's Hospital, and the investigators adhered to the ethical principles of the Declaration of Helsinki when conducting the study.

Patients who had received hemodialysis therapy at the dialysis center in Peking University People's Hospital were checked for enrollment from October 2011 to December 2017. Inclusion criteria were age ≥18 years, chronic maintenance dialysis for at least 3 months, mental competence, use of UFH or LMWH as an anticoagulant during dialysis, and willingness to participate in the study. Exclusion criteria included systemic illnesses or organ diseases that may affect bone (except diabetes mellitus), clinical conditions that may limit study participation (e.g., cardiovascular disease and infections), chronic alcoholism, and drug addiction.

Patient grouping according to heparin usage

The type of heparin used for each patient during the 2-year follow-up was retrieved from the medical chart. Patients were grouped as UFH users (provided with UFH in more than 80% dialysis sessions) and LMWH users (provided with LMWH in more than 80% dialysis sessions). Patients who used both UFH and LMWH were excluded.

Demographics and clinical indices

Patient age, sex, primary causes of uremia, dialysis duration, and body mass index (BMI) were collected at baseline. Clinical indices including hemoglobin (Hb, g/dL), albumin (Alb, g/dL), corrected calcium (cCa, mmol/L), phosphorus (P, mmol/L), alkaline phosphatase (ALP, U/L), and intact PTH (iPTH, pg/ml) were also collected at baseline and at the end of follow-up. Blood samples were taken immediately before the dialysis session.

Bone mineral density measurement

Enrolled patients received DXA to evaluate BMD at baseline and 2 years later. DXA was used to assess the lumbar spine (from L1 through L4) and the left proximal femur (femoral neck) BMD. BMD was measured with a Hologic Delphi QDR Series (HOLOGIC Inc., Waltham, USA). BMD was reported in absolute values (g/cm^2). T-score was calculated based on comparison with a 30-year-old reference group and Z-score was based on comparison with age- and sex-matched reference group.[20] Osteoporosis was defined as a T-score ≤ −2.5 at least one site (lumbar spine and/or femoral neck), and osteopenia as T-score between −1.0 and −2.5.

Statistical analyses

Continuous data are shown as mean ± standard deviation (SD) and categorical data as percentages. Nonparametric data are expressed as median and 25th to 75th interquartile range (IQR25-75). Analyses were conducted using SPSS version 22 software (IBM SPSS, USA). Continuous data were evaluated for normality before statistical testing. The Mann-Whitney test was used for non-normally distributed continuous variables and the t test for normally distributed continuous variables. The chi-square test was used for categorical variables. Spearman or Pearson correlation analysis was used to test the relationship between the clinical indices and changes in BMD (in g/cm^2), T-score, and Z-score (BMDs) depending on the distribution and equality of variance. Six multiple linear regression models were built to explore the relationship between heparin type and each change in BMD at the lumbar spine and femur neck after adjusting for cCa, P, DM, and iPTH. For each test, a P value less than 0.05 was considered as statistically significant.

RESULTS

Study cohort description

Patient demographics, clinical indices, and diagnosis according to BMD at baseline and 2 years are shown in Table 1. A total of 104 patients undergoing MHD were enrolled at baseline, 32 patients were excluded, and 72 patients completed BMD measurements 2 years later. Reasons for exclusion included 15 patients did not have the second BMD measurement, six patients died, three patients received kidney transplantation, and eight patients withdrew due to transferring to another hospital or personal reasons. The study was conducted on 72 HD patients, including 32 (44.44%) female patients, with an average age of 59.75 ± 15.18, and a median dialysis duration of 17.00

(7.25, 57.75) months. Eighteen (25.00%) patients had complications of diabetes mellitus. Among the patients, 38 (52.78%) had osteopenia, 20 (27.78%) osteoporosis, and 14 (19.44%) had normal bone mass at baseline. After 2 years, the number changed to 38 (52.78%) with osteopenia, 23 (31.94%) osteoporosis, and 11 (15.28%) normal bone mass. There were no significant difference in demographics, proportion of DM, data on BMD at different sites, and clinical indices of serum such as Hb, P, ALP, and iPTH between the two groups. The serum cCa level was higher 2 years later (P = 0.009). BMDs at the lumbar spine and femoral neck are shown in Figure 1.

Table 1 Population characteristics, clinical indices, and BMD in patients undergoing MHD at baseline and 2 years

	At baseline (n = 72)	At 2 years (n = 72)
Age	59.75 ± 15.18	61.75 ± 15.18
Dialysis vintage (months)	17.00 (7.25, 57.75)	41.00 (30.25, 83.00)
Female, n (%)	32 (44.44)	32 (44.44)
DM, n (%)	18 (25.00)	18 (25.00)
BMI	23.48 ± 3.48	24.05 ± 3.74
Hb (g/L)	110.94 ± 9.85	114.35 ± 6.66
Alb (g/L)	39.85 ± 3.04	39.64 ± 2.86
cCa (mmol/L)	2.22 ± 0.14	2.31 ± 0.23*
P (mmol/L)	1.55 ± 0.44	1.60 ± 0.48
iPTH (pg/ml)	202.47 ± 144.52	199.02 ± 149.72
ALP (U/L)	68.34 (59.00, 81.88)	76.43 ± 28.58
BMD at lumbar spine (g/cm^2)	0.93 ± 0.13	0.94 ± 0.17
T score of lumbar spine	−1.28 ± 1.18	−1.19 ± 1.39
Z score of lumbar spine	−0.35 ± 1.22	−0.24 ± 1.4
BMD at femur neck (g/cm^2)	0.68 ± 0.15	0.67 ± 0.14
T score of femur neck	−1.70 ± 1.21	−1.79 ± 1.14
Z score of femur neck	−0.70 ± 1.08	−0.74 ± 1.05
Diagnosis		
Normal bone mass, n (%)	14 (19.44)	11 (15.28)
Osteopenia, n (%)	38 (52.78)	38 (52.78)
Osteoporosis, n (%)	20 (27.78)	23 (31.94)

*P < 0.05.
Alb = albumin; ALP = alkaline phosphatase; BMD = bone mineral density; BMI = body mass index; cCa = corrected calcium; DM = diabetes mellitus; Hb = hemoglobin; iPTH = intact parathyroid hormone; P = phosphate.

Characteristics and BMD in UFH and LMWH groups

Characteristics and BMD values of patients using UFH and LMWH at baseline and 2 years later are shown in Table 2. Excluding six patients who used both UFH and LMWH, 40 (60.61%) were UFH users, and 26 (39.39%) were LMWH users. In the LMWH group (n = 26), 24 (92.31%) were nadroparin users, and 2 (7.69%) were provided nadroparin in more than 80% dialysis sessions (but provided enoxaparin for the rest of dialysis sessions). The primary causes of uremia predominantly included chronic glomerulonephritis (n = 32, 48.48%), diabetic nephropathy (n = 14, 21.21%), hypertensive renal disease (n = 7, 10.6%), chronic tubulointerstitial nephropathy (n = 4, 6.1%), and others (n = 9, 13.64%). There were no significant differences in any demographic characteristics or clinical indices between the two groups. In addition, BMD and related diagnosis showed no significant difference either (Table 2). After 2 years, although BMD decreased in some patients in the UFH group, a slight increase in BMD was observed in the LMWH group. The mean changes in BMD (in g/cm^2) [0(−0.03,0.04) vs. 0.04(0,0.06), P = 0.023], T-score [0(−0.40,0.30) vs. 0.35(−0.03,0.53), P = 0.038], and Z-score [0.10(−0.30,0.40) vs. 0.45(0.08,0.63), P = 0.031] in the lumbar spine in the UFH group were lower than those in the LMWH group. (Table 3). Femur neck BMD did not change significantly.

Progression of bone loss

Clinical parameters were compared between patients with bone loss progression and those without (Table 4). Of the 66 patients, 9 (13.64%) had bone loss progression and 57 (86.36%) did not have progression. No significant differences in demographic characteristics and clinical indices (except P 2 years later) were found between the progression and nonprogression groups. The serum P level was higher in the progression group (P = 0.037).

Factors affecting BMD changes

The correlation analysis of BMD changes, clinical indices, and heparin substance dosage was evaluated using Spearman's rank correlations at the lumbar spine and femoral neck (Table 5). The results indicated that changes in BMD at the lumbar spine had significant negative associations with P (Table 5).

The results of multiple linear regression analyses are shown in Table 6. We found that P was a negative independent risk factor associated with the changes in BMD (in g/cm^2) (β = −0.293, P = 0.025), T-score (β = −0.283, P = 0.031), and Z-score (β = −0.284, P = 0.030) at the lumbar spine. DM was another independent risk factor associated with changes in BMD (in g/cm^2) (β = 0.269, P = 0.035), T-score (β = 0.256, P = 0.043), and Z-score (β = 0.274, P = 0.029) at the femoral neck. However, the
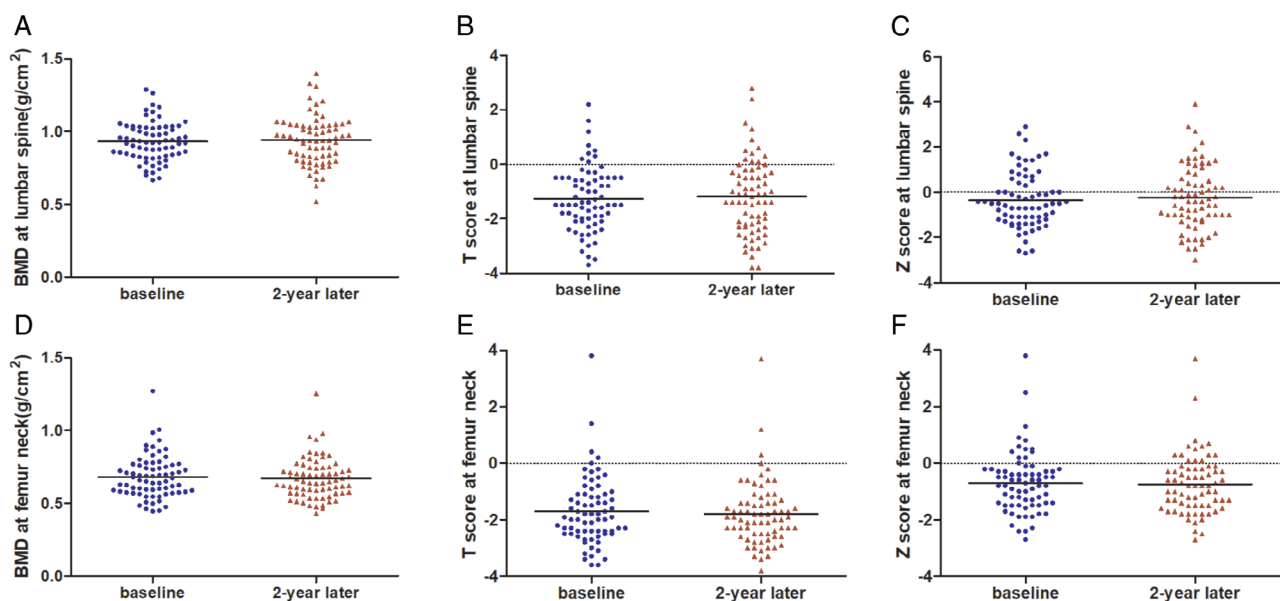
Figure 1 BMD, T-score, and Z-score at the lumbar spine and femoral neck at baseline and 2 years. (A)–(C) BMD (in g/cm^2), T-score and Z-score at the lumbar spine; (D)–(F) BMD (in g/cm^2), T-score and Z-score at the femoral neck. BMD: bone mineral density. [Color figure can be viewed at wileyonlinelibrary.com]

Table 2 Characteristics and BMD in UFH and LMWH groups at baseline and 2 years

	UFH	LMWH	*P* value
	(n = 40)	(n = 26)	
Female, n (%)	21 (52.50)	8 (30.77)	0.127
DM, n (%)	10 (25.00)	8 (30.77)	0.778
Primary causes of uremia, n (%)			
CGN	21 (52.50)	11 (42.31)	0.218
DN	7 (17.50)	7 (26.92)	
HN	6 (15.00)	1 (3.85)	
CIN	3 (7.50)	1 (3.85)	
Others	3 (7.50)	6 (23.08)	
Age (years)	61.6 ± 15.07	62.85 ± 15.80	0.684
Dialysis vintage (months)	17.50 (5.00, 64.75)	15.50 (8.75, 28.25)	0.713
BMI	23.21 ± 3.20	23.8 ± 3.60	0.616
Baseline values			
cCa (mmol/L)	2.22 ± 0.16	2.22 ± 0.13	0.573
P (mmol/L)	1.58 ± 0.44	1.52 ± 0.45	0.806
iPTH (pg/ml)	187.68 ± 121.62	220.95 ± 170.51	0.197
ALP (U/L)	69.67 (57.13, 82.38)	65.00 (57.42, 82.38)	0.627
Alb (g/L)	40.01 ± 2.46	40.29 ± 2.44	0.797
Hb (g/L)	108.95 ± 11.21	113.75 ± 7.32	0.061
BMD at lumbar spine (g/cm^2)	0.92 ± 0.13	0.94 ± 0.12	0.722
T score	−1.35 ± 1.12	−1.21 ± 1.05	0.768
Z score	−0.70 (−1.30, 0.68)	−0.40 (−0.83, 0)	0.550
BMD at femur neck (g/cm^2)	0.68 ± 0.15	0.69 ± 0.12	0.598
T score	−1.68 ± 1.34	−1.71 ± 0.91	0.429
Z score	−0.80 (−1.50, −0.30)	−0.60 (−1.25, −0.28)	0.948
Diagnosis			0.315
Normal bone mass, n (%)	7 (17.50)	5 (19.23)	
Osteopenia, n (%)	20 (50.00)	17 (65.38)	
Osteoporosis, n (%)	13 (32.50)	4 (15.38)	
Two-year values			
cCa (mmol/L)	2.33 (2.33, 2.46)	2.29 (2.22, 2.41)	0.416
P (mmol/L)	1.63 ± 0.49	1.58 ± 0.44	0.960
iPTH (pg/ml)	178.98 (62.62, 294.05)	131.2 (64.51, 255.26)	0.723
ALP (U/L)	70.2 (61.50, 94.67)	68.50 (51.94, 82.75)	0.279
Alb (g/L)	39.55 ± 2.41	40.33 ± 2.02	0.582
Hb (g/L)	114.48 ± 6.58	114.92 ± 4.86	0.407
BMD at lumbar spine (g/cm^2)	0.92 ± 0.16	0.97 ± 0.14	0.428
T score	−1.34 ± 1.24	−1 ± 1.26	0.589
Z score	−0.71 ± 1.17	−0.73 ± 0.86	0.150
BMD at femur neck (g/cm^2)	0.66 (0.58, 0.72)	0.64 (0.57, 0.77)	0.713
T score	−1.95 (−2.50, −1.43)	−1.95 (−2.53, −1.10)	0.674
Z score	−0.71 ± 1.17	−0.73 ± 0.86	0.631
Diagnosis			0.640
Normal bone mass, n (%)	4 (10.00)	5 (19.23)	
Osteopenia, n (%)	23 (57.50)	14 (53.85)	
Osteoporosis, n (%)	13 (32.50)	7 26.92)	

Alb = albumin; ALP = alkaline phosphatase; BMD = bone mineral density; BMI = body mass index; cCa = corrected calcium; CGN = chronic glomerulonephritis; CTIN = chronic tubulointerstitial nephropathy; DM = diabetes mellitus; DN = diabetic nephropathy; Hb = hemoglobin; HN = hypertensive nephropathy; iPTH = intact parathyroid hormone; P = phosphate; UFH = unfractionated heparin; LMWH = low-molecular-weight heparin. In the LMWH group (n = 26), 24(92.31%) were nadroparin users and 2(7.69%) were provided nadroparin in more than 80% dialysis sessions (but provided Enoxaparin for the rest dialysis sessions).

Table 3 BMD changes between UFH and LWMH groups

	UFH (n = 40)	LMWH (n = 26)	*P* value
ΔBMD at lumbar spine (g/cm^2)	0 (−0.03, 0.04)	0.04 (0, 0.06)	0.023*
ΔT score	0 (−0.40, 0.30)	0.35 (−0.03, 0.53)	0.038*
ΔZ score	0.10 (−0.30, 0.40)	0.45 (0.08, 0.63)	0.031*
ΔBMD at femur neck (g/cm^2)	−0.02 (−0.04, 0.01)	0 (−0.03, 0.03)	0.412
ΔT score	−0.1 (−0.30, 0)	0 (−0.20, 0.20)	0.256
ΔZ score	0 (−0.20, 0.10)	0.10 (−0.13, 0.30)	0.406
Progression of bone loss, n (%)	6 (15.00)	3 (11.54)	1.000

*$P < 0.05$.

Δ represented the changes in BMD within 2 years. BMD = bone mineral density; UFH = unfractionated heparin; LMWH = low-molecular-weight heparin. In the LMWH group (n = 26), 24(92.31%) were nadroparin users and 2(7.69%) were provided Nadroparin in more than 80% dialysis sessions (but provided Enoxaparin for the rest dialysis sessions).

Table 4 Comparison of demographic, clinical indices and doses of heparin substances in two groups

	Progression	Non-progression	*P* value
	(n = 9)	(n = 57)	
Female, n (%)	4 (44.44)	25 (43.86)	1.000
DM, n (%)	4 (44.44)	13 (22.81)	0.220
Age (years)	58.22 ± 18.07	62.7 ± 14.86	0.495
Dialysis vintage (months)	30.00 (26.50, 100.50)	41.00 (31.00, 82.75)	0.489
BMI	23.81 ± 3.45	24.11 ± 3.72	0.674
Baseline values			
cCa (mmol/L)	2.26 ± 0.14	2.22 ± 0.15	0.525
P (mmol/L)	1.67 ± 0.51	1.54 ± 0.43	0.531
iPTH (pg/ml)	199.85 (88.21, 311.85)	186.60 (93.80, 253.14)	0.607
ALP (U/L)	68.88 ± 16.49	73.78 ± 26.14	0.779
Alb (g/L)	39.57 ± 2.65	40.2 ± 2.42	0.438
Hb (g/L)	108.01 ± 11.63	111.29 ± 9.86	0.531
Two-year values			
cCa (mmol/L)	2.37 ± 0.17	2.3 ± 0.24	0.184
P (mmol/L)	1.86 ± 0.28	1.57 ± 0.48	0.037*
iPTH (pg/ml)	236.2 (165.64, 441.85)	137.58 (60.67, 263.39)	0.123
ALP (U/L)	77.00 (65.00, 106.38)	69.00 (57.25, 82.00)	0.178
Alb (g/L)	39.26 ± 2.07	39.95 ± 2.31	0.355
Hb (g/L)	113.44 ± 5.94	114.85 ± 5.96	0.601

*$P < 0.05$.

Alb = albumin; ALP = alkaline phosphatase; BMI = body mass index; cCa = corrected calcium; DM = diabetes mellitus; Hb = hemoglobin; iPTH = intact parathyroid hormone; P = phosphate; UFH = unfractionated heparin; LMWH = low-molecular-weight heparin.

type of heparin substance was not correlated with BMD changes (Table 6).

DISCUSSION

Long-term use of heparin is associated with bone loss, osteoporosis, and fracture in nondialysis patients.[15] In this study, we found that UFH might be related to the loss of lumbar spine BMD in patients undergoing MHD. However, we did not find evidence that the type of heparin substance was correlated with the progression of bone loss in patients undergoing MHD in our center.

CKD-MBD, which is common among patients undergoing MHD, results in an increased risk of fracture and mortality.[1] Among the 72 patients undergoing MHD, 58(80.56%) cases at baseline had osteopenia and osteoporosis in accordance to the diagnostic criteria, suggesting that patients undergoing MHD have a high risk of decreased BMD (Table 1). A total of 66 patients undergoing MHD using UFH and LMWH and took the BMD test twice completed the follow-up study. The

Table 5 Correlation analysis of BMD changes and clinical indices

	ΔBMD at lumbar spine (g/cm²)		ΔT score		ΔZ score		ΔBMD at femur neck (g/cm²)		ΔT score		ΔZ score	
	r	P value	r	P value	r	P value	r	P value	r	P value	r	P value
P	−0.268	0.031*	−0.276	0.026*	−0.277	0.026*	−0.169	0.176	−0.156	0.211	−0.199	0.108
cCa	−0.065	0.609	−0.053	0.672	−0.065	0.605	−0.163	0.192	−0.187	0.133	−0.205	0.098
ALP	−0.065	0.606	−0.117	0.353	−0.105	0.407	−0.037	0.766	−0.068	0.588	−0.056	0.653

*$P < 0.05$.
Δ represented the changes in BMD within 2 years. BMD = bone mineral density; P = phosphate; UFH = unfractionated heparin; LMWH = low-molecular-weight heparin.

Table 6 Multiple linear regression analytical method analyzed the independent risk factors of BMD changes

	Variable	β	T	P value
ΔBMD at lumbar spine (g/cm²)	P	−0.293	−2.302	0.025*
	cCa	−0.083	−0.674	0.503
	iPTH	0.053	0.422	0.675
	DM	−0.142	−1.144	0.257
	Heparin type	0.132	1.075	0.287
ΔT score	P	−0.283	−2.212	0.031*
	cCa	−0.052	−0.423	0.674
	iPTH	0.077	0.608	0.546
	DM	−0.012	−0.099	0.921
	Heparin type	0.175	1.417	0.162
ΔZ score	P	−0.284	−2.226	0.030*
	cCa	−0.058	−0.472	0.639
	iPTH	0.033	0.262	0.794
	DM	−0.007	−0.053	0.958
	Heparin type	0.181	1.465	0.148
ΔBMD at femur neck (g/cm²)	P	−0.064	−0.501	0.618
	cCa	0.010	0.081	0.936
	iPTH	−0.106	−0.834	0.408
	DM	0.269	2.157	0.035*
	Heparin type	0.037	0.301	0.764
ΔT score	P	−0.072	−0.566	0.574
	cCa	0.010	0.084	0.933
	iPTH	−0.128	−1.017	0.313
	DM	0.256	2.063	0.043*
	Heparin type	0.102	0.829	0.411
ΔZ score	P	−0.101	−0.801	0.426
	cCa	0.014	0.115	0.909
	iPTH	−0.150	−1.210	0.231
	DM	0.274	2.238	0.029*
	Heparin type	0.077	0.638	0.526

*$P < 0.05$.
Δ represented the changes in BMD within 2 years. BMD = bone mineral density; cCa = corrected calcium; DM = diabetes mellitus; iPTH = intact parathyroid hormone; P = phosphate.

results showed that there was no significant difference in baseline and 2-year values between the UFH and LMWH groups. However, changes in BMD (in g/cm²), T-score, and Z-score at lumbar spine in the UFH group decreased significantly compared to those in the LMWH group in 2 years. This indicated that UFH might be correlated with lumbar spine loss in patients undergoing MHD compared with LMWH. A similar result was found

wherein the mean BMD of the lumbar spine was significantly lower in the UFH group than in the LMWH group in women 3 years after delivery according to Pettilä et al.[21] We did not observe a significant difference in bone loss progression at the femur neck between the UFH and LMWH groups.

Clinical trials and animal experiments have demonstrated that long-term use of heparin can induce bone loss and osteoporosis, and a high cumulative dosage of heparin was related to the progression of bone loss.[17, 18, 22] However, our results were negative. The reasons were as follows: (1) The follow-up period was not long enough. Osteoporosis in CKD is a complication with many influencing factors. It has a long progression and changes slowly. Meng et al. demonstrated that there was no difference in BMD between UFH and LMWH group in rats after a 6-week intervention.[23]

Similar results were reported in the study by Matzsch et al.[18] In our research, lumbar spine BMD changes were significantly different between the UFH and LMWH groups (Table 3). A prolonged follow-up period might lead to additional observations. (2) Low dosage and little difference in the dosage of UFH or LMWH might be another reason. In previous studies, UFH and LMWH used were usually over 10,000 IU and 5000 IU per day for several months to treat thrombosis.[24] However, marginal dosage of UFH or LMWH during dialysis sessions were usually used. The effect of low doses of UFH or LMWH might be small and undetectable. In addition, the difference in the dosage of either UFH or LMWH was small among patients. The narrow range also made it challenging to determine the relationship between doses of UFH or LMWH and BMD changes. (3) Receiving calcium or vitamin D supplements or phosphate binders and participating in physical activity may impact BMD. In a study by Cianciolo et al., active vitamin D increased BMD after renal transplantation.[25] Zhang indicated that lanthanum carbonate could improve bone density in patients with diabetes undergoing MHD.[26] Dolgos et al. followed 133 renal transplant patients, stating that physical activity was associated with high BMD shortly after renal transplantation.[27] We observed increased BMD in some participants after 2 years (Table 3). The comprehensive effect of oral medication and physical activity may play an important role.

Our results also found that some factors were related to the progression of bone loss, including diabetes mellitus and phosphate. These findings were consistent with those of previous studies. Both type 1 and type 2 diabetes mellitus are associated with low BMD, and an increased fracture risk is well documented.[28] Vestergaard showed that patients with diabetes had decreased BMD

and increased fracture risk.[29] Furthermore, an increased level of phosphate could predict a low level of lumbar spine BMD, which is similar to Campos-Obando et al.[30]

Our study had several limitations. First, the sample size was small and the follow-up period was short. A larger sample size might help us conduct a stratified analysis of different LMWH forms. Longer time might be needed to detect the progression of osteoporosis. Second, some participants were receiving calcium or vitamin D supplements or phosphate binders, but information on drug intervention and physical activity were not included in the analysis.

In summary, UFH might be associated with loss of lumbar spine BMD in patients undergoing MHD. Further studies with larger sample sizes and longer follow-up periods are needed to confirm the effect of heparin substances on BMD in patients undergoing MHD.

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