

Low Molecular Weight Heparins and Antiplatelet Drugs, and Bone Mineral Density in Dialysis Patients

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Variations in results concerning the influence of low molecular weight heparins (LMWHs) and antiplatelet drugs (APtDs) on bone mineral density (BMD) have led us to investigate whether dialysis patients receiving these drugs (group I) are characterized by a BMD different from that of patients not receiving such medications (group II).

Group I consisted of 14 patients [mean age: 64.7 ± 16.0 years; 4 on hemodialysis (HD), 10 on peritoneal dialysis (PD); dialysis duration: 22.7 months (range: 7.9 – 59.6 months)] who were regularly receiving LMWHs (4 HD patients) or APtDs (10 PD patients, 1 HD patient), or both, for at least 2 years. Group II consisted of 16 PD patients [mean age: 48.7 ± 16.2 years; dialysis duration: 16.3 months (6.3 – 45.5 months)]. We evaluated BMD as assessed in the femoral neck and lumbar spine, serum parathyroid hormone, blood pH, and parameters of calcium-phosphate balance and nutritional state, and compared values between the two groups.

As compared with group II, group I had significantly lower measurements in the femoral neck: BMD (0.711 ± 0.100 g/cm² vs. 0.904 ± 0.124 g/cm², $p = 0.000$), T score [-2.38 (range: -4.06 to -1.27) vs. -0.71 (range: -3.05 to 2.37), $p = 0.000$], Z score [-1.34 (range: -2.36 to -0.15) vs. 0.12 (range: -1.0 to 2.97), $p = 0.001$], BMD as a percentage of peak bone mass ($69.1\% \pm 9.0\%$ vs. $94.4\% \pm 16.6\%$, $p = 0.000$), BMD as a percentage age norm ($81.6\% \pm 9.7\%$ vs. $103.4\% \pm 18.5\%$, $p = 0.000$). We observed no other significant differences in examined parameters between the groups.

Dialysis patients regularly receiving LMWHs or APtDs, or both, show lower BMD measures in the femoral neck; they therefore require more frequent

monitoring of BMD and timely prophylaxis against osteoporosis.

Key words

Anticoagulants, bone mineral density

Introduction

Low molecular weight heparins (LMWHs) are frequently used in patients treated with intermittent hemodialysis (IHD) for prevention of blood clots in the extracorporeal circuit. Antiplatelet drugs (APtDs) are administered in both IHD and peritoneal dialysis (PD) patients for treatment of cardiovascular diseases or preservation of vascular graft or catheter function. Among the ADtPs, aspirin is the most frequently used; ticlopidine, clopidogrel, dipyridamole, and sulfipyrazone are prescribed less frequently (1).

Published results indicate either decreased bone mineral density (BMD) in people chronically receiving anticoagulants (2–4) or no such effect (5,6). Heparin is suggested to influence bone tissue formation and to enhance its resorption, but a mechanism of its influence on bone tissue remains unclear. A dose-dependent influence of heparins on the formation and function of osteoclasts was shown (7). Other studies revealed a less deleterious influence of LMWHs than of unfractionated heparin on bone (8,9).

Acetylsalicylic acid inhibits cyclo-oxygenase (COX) and reduces production of prostaglandins, which are involved in regulation of bone turnover. Two isoforms of COX are known: COX-1 and COX-2. Production of prostaglandins associated with bone loss is primarily mediated through the COX-2 pathway. Aspirin may also have effects on bone independent of the prostaglandin pathway (10).

In the available literature, we found no data on the association between ticlopidine administration and BMD.

Independent of the mechanism of action of the aforementioned drugs, their administration effects a

change in the properties of the blood: specifically, a lesser ability to clot in the blood vessels. The scientific literature contains little data concerning changes in BMD in dialyzed patients who are chronically receiving LMWHs or APtDs, or both (6). Reports indicating an influence of LMWHs and APtDs on BMD led us to investigate whether dialysis patients receiving these drugs are characterized by a BMD different from that of patients not receiving such medication.

Patients and methods

Uremic patients older than 18 years treated with PD or IHD were qualified for the study. Patients that met at least one of the following conditions were excluded:

- Dialysis treatment for less than 6 months
- Parathyroidectomy during the last 6 months,
- Recognized disease (except diabetes mellitus) that is not a complication of uremia or dialysis treatment and that could influence bone metabolism (for example, primary gout, rheumatoid arthritis, thyroid gland imbalances, tumors)
- Implanted medical devices (for example, pacemaker, infusion pump)
- Medication with drugs that influence bone metabolism (for example, glucocorticosteroids, estrogens, androgens) currently and within 2 months of the study examination
- Acute infection or inflammation during the month preceding the study examination

We studied 30 patients who met the preceding criteria. These patients were allocated to two groups. Group I included patients who had regularly been receiving LMWHs (nadroparin calcium or enoxaparin) or APtDs, or both, for at least 2 years. Group II consisted of patients who were not receiving LMWHs or APtDs. Group I consisted of 14 patients [mean age: 64.7 ± 16.0 years; 4 on IHD, 10 on PD; dialysis duration: 22.7 months (range: 7.9–59.6 months)]. Group II consisted of 16 PD patients [mean age: 48.7 ± 16.2 years; dialysis duration: 16.3 months (range: 6.3–45.5 months)].

In group I, LMWHs were administered in 4 HD patients every week during each of 3 IHD sessions lasting 4 hours each. Individual doses were sufficient for avoiding blood clotting in the dialyzer. With regard to APtDs, acetylsalicylic acid 75 mg daily was taken by 10 PD patients, and ticlopidine 250 mg twice daily

by 1 HD patient. Table I presents the clinical characteristics of the study patients.

We assessed BMD by dual-energy X-ray absorptiometry in the femoral neck and the L2–L4 lumbar region. Serum intact parathyroid hormone, calcium–phosphate balance, blood pH, serum markers of inflammation, serum and anthropometric markers of nutrition status, and bioimpedance records of body composition were evaluated and compared between the two groups.

In PD patients, study measurements were performed with a “dry” peritoneal cavity after drainage of dialysate, which was not replaced until completion of all study procedures. In IHD patients, a blood sample was taken before the midweek IHD session; other examinations were started at 30 minutes after the IHD session.

We used the Shapiro–Wilks test to check the normality of distribution of the variables for each group separately. Results are expressed as mean \pm 1 standard deviation, or as median and range, as appropriate. Comparisons between the groups for non adjusted results were performed using the Student *t*-test for unpaired data if distribution in both groups was normal, or by the Mann–Whitney test if a normal distribution was not present. Results adjusted for sex, age, coffee consumption, and use of sedatives, corticosteroids, nonsteroidal anti-inflammatories, and anti-epilepsy drugs were compared using analysis of covariance methodology. The prevalence of variables in both groups was assessed by the chi-square test with Yates correction. A *p* value below 0.05 was judged to be significant. The statistical analyses were performed using Statistica 7.1 (StatSoft, Tulsa, OK, U.S.A.).

Results

The study groups did not differ in sex distribution and dialysis duration, but patients receiving anticoagulants (group I) were significantly older ($p = 0.012$) than patients not taking these drugs (group II). Adjustment for coffee consumption and use of sedatives, corticosteroids, nonsteroidal anti-inflammatories, and anti-epilepsy drugs did not show a significant difference in metrical age between the groups.

As compared with group II, group I displayed significantly lower BMD measured in the femoral neck (Figure 1). Mean neck T score indicated osteopenia in anticoagulant recipients; in non recipients, it was in

TABLE I Clinical characteristics of the study patients

<i>Characteristic</i>	<i>All patients (n=30)</i>	<i>Group I (n=14)</i>	<i>Group II (n=16)</i>	<i>Group I vs. II (p value)</i>
Causes of ESRD [n (%)]				
Chronic tubulointerstitial nephritis	8 (26.7)	3 (21.4)	5 (31.2)	0.8469
Diabetic nephropathy	7 (23.3)	5 (35.7)	2 (12.5)	0.2859
Chronic glomerulonephritis	5 (16.7)	1 (7.1)	4 (25.0)	0.4132
Polycystic kidney disease	4 (13.3)	1 (7.1)	3 (18.7)	0.6930
Hypertensive nephropathy	1 (3.3)	1 (7.1)	—	0.9458
Obstructive nephropathy	1 (3.3)	1 (7.1)	—	0.9458
Unknown	4 (13.3)	2 (14.3)	2 (12.5)	0.6930
Cardiac diseases [n (%)]				
Ischemic heart disease	11 (36.7)	8 (57.1)	3 (18.7)	.0723
Myocardial infarction	1 (3.3)	1 (7.1)	—	0.9458
Revascularization	1 (3.3)	1 (7.1)	—	0.9458
Atherosclerotic cardiomyopathy	2 (6.7)	1 (7.1)	1 (6.2)	0.5249
Persistent atrial fibrillation	1 (3.3)	1 (7.1)	—	0.9458
Paroxysmal atrial fibrillation	1 (3.3)	—	1 (6.2)	0.9458
Hypertrophic cardiomyopathy	1 (3.3)	1 (7.1)	—	0.9458
Mitral insufficiency	1 (3.3)	—	1 (6.2)	0.9458
Congestive heart failure [n (%)]				
NYHA I–III	13 (43.3)	8 (57.1)	5 (31.2)	0.2898
NYHA I	1 (3.3)	1 (7.1)	—	0.9458
NYHA II	8 (26.7)	4 (28.6)	4 (25.0)	0.8469
NYHA III	4 (13.3)	3 (21.4)	1 (6.2)	0.4954
Arterial hypertension	26 (86.7)	12 (85.7)	14 (87.5)	0.6930

ESRD = end-stage renal disease; NYHA = New York Heart Association.

the normal range (Figure 2). The BMD as a percentage of peak bone mass for young adults (Figure 3), the BMD as a percentage of age norm (Figure 4), and the Z score (Figure 5) were also significantly lower in anticoagulant recipients. After adjustment of the results for sex, age, coffee consumption, and use of sedatives, corticosteroids, nonsteroidal anti-inflammatories, and anti-epilepsy drugs, the differences between the groups in femoral neck BMD remained statistically significant.

Group I contained no patients with a normal BMD in the femoral neck as indicated by T score value. Anticoagulant recipients had osteopenia or osteoporosis in the femoral neck. In the lumbar region, results were not so clear, but osteoporosis occurred only in anticoagulant recipients (Table II).

Parameters of BMD in the lumbar region were not significantly different between groups, but they were consistently lower in anticoagulant recipients. There were no significant differences between the groups in calcium–phosphate balance, blood pH, and blood count. Values for C-Reactive protein, serum lipids, and anthropometric and bioimpedance measurements were also not significant between groups (Table III).

Discussion

Bone mineral density depends on many endogenous and exogenous factors. Data from the scientific literature indicate the influence of anticoagulants on BMD in patients who need anticoagulant treatment or prophylaxis. Results of investigations have shown a decrease of BMD in the L2–L4 lumbar region in patients on prolonged acenocoumarol therapy for cardiac failure (4); a decrease of BMD by 3.05% in patients on secondary anticoagulant prophylaxis with LMWHs or acenocoumarol (2); and a modest but progressive decrease in BMD, more evident in patients on LMWHs than on acenocoumarol, in people on treatment and prophylaxis of venous thromboembolism (3).

On the other hand, a reduction in BMD was not observed in patients treated for 8 months with IHD with the use of LMWHs (6). Bone loss in the lumbar spine during pregnancy associated with the use of LMWHs plus low-dose aspirin because of antiphospholipid syndrome was not significantly different from physiologic bone loss in women (5).

The results obtained in the present study indicate that, in dialysis patients, treatment with anticoagulants

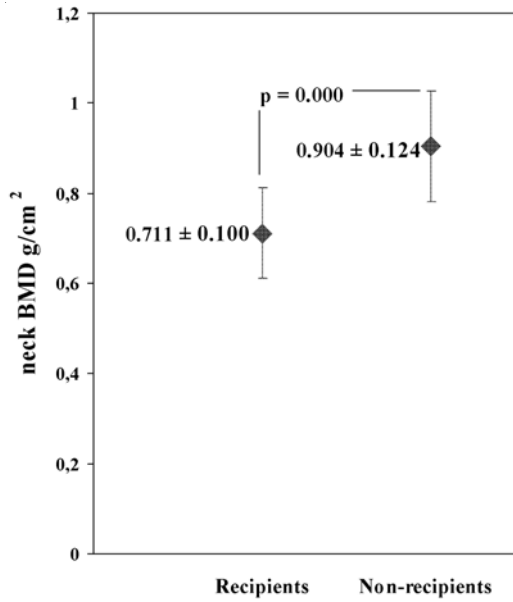


FIGURE 1 Femoral neck bone mineral density (BMD) in dialyzed patients taking (“recipients”) or not taking (“non recipients”) anticoagulants.

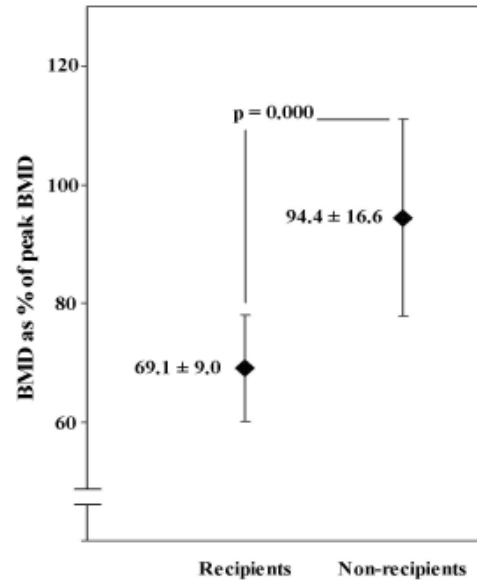


FIGURE 3 Femoral neck bone mineral density (BMD) as a percentage of peak BMD of young adults in dialyzed patients taking (“recipients”) or not taking (“non recipients”) anticoagulants.

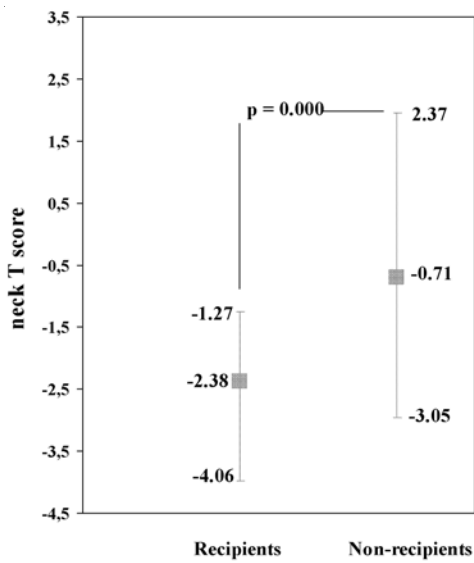


FIGURE 2 Femoral neck T score in dialyzed patients taking (“recipients”) or not taking (“non recipients”) anticoagulants.

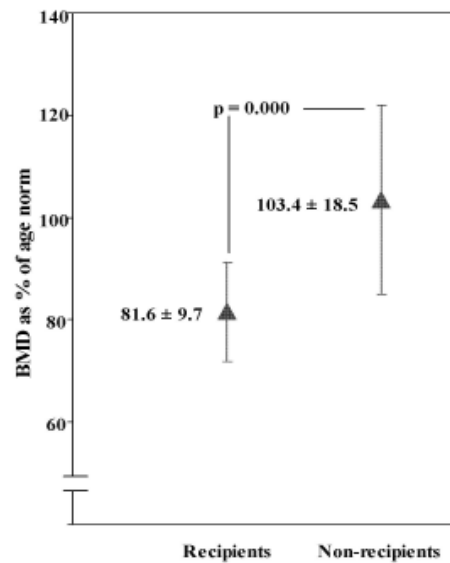


FIGURE 4 Femoral neck bone mineral density (BMD) as a percentage of age norm in dialyzed patients taking (“recipients”) or not taking (“non recipients”) anticoagulants.

may influence BMD loss in the femoral neck. The non-significantly different results in parameters of inflammatory status, uremic toxicity, calcium–phosphate balance, nutrition status, and bioimpedance-measured body composition indicate similarity in both groups of dialysis patients treated for a comparable period of time. It is, however, notable that differences in the duration of the use or non use of anticoagulants were significantly greater than those for dialysis duration, because even patients dialyzed for 6 – 7 months had been treated with LMWHs or APtDs, or both, for at least 2 years.

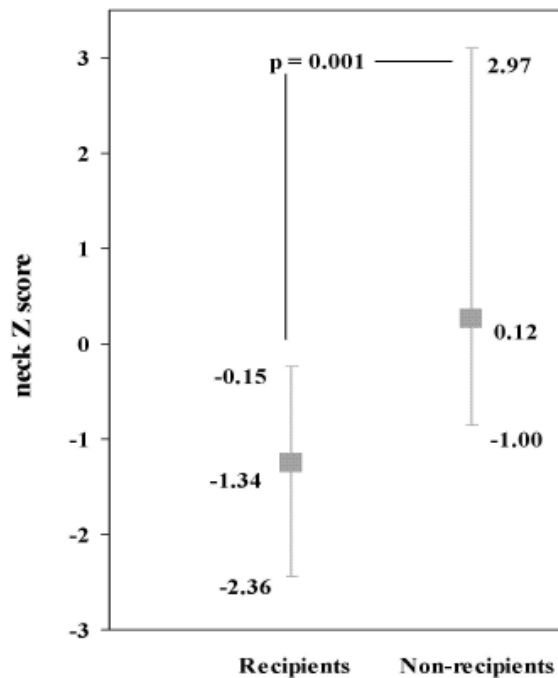


FIGURE 5 Femoral neck Z score in dialyzed patients taking (“recipients”) or not taking (“non recipients”) anticoagulants.

Serum lipid profiles were also not significantly different between the groups, although LMWHs are known to possibly positively modify serum concentrations of lipids in IHD patients, at least as compared to a period of administration of unfractionated heparin (6). Additionally, the use of multivariate analysis eliminated the influence of some factors that are known to change BMD on the significance of the differences in BMD parameters in the study groups. These factors included sex, age, coffee consumption, and use of sedatives, corticosteroids, nonsteroidal anti-inflammatories, and anti-epilepsy drugs (11,12). In the examined patients, we previously showed the negative influence of age and sex on femoral neck BMD and of coffee consumption on BMD in the lumbar region (13,14). After adjustment of the results in the present study for those confounders, and additionally for the use of sedatives, corticosteroids, nonsteroidal anti-inflammatories, and anti-epilepsy drugs, the differences between the groups in the femoral neck BMD remained statistically significant.

Conclusions

In agreement with data from the literature, dialyzed patients receiving LMWHs or APtDs require more frequent monitoring of BMD, just as do patients treated with such drugs for venous thromboembolism or for secondary venous thromboembolic prophylaxis (3). In contrast to non dialyzed cardiac patients receiving acenocoumarol (4), dialyzed patients taking LMWHs or APtDs, or both, did not show lower BMD in the L2–L4 region, but did show a difference in femoral neck BMD.

The results obtained in the present study indicate that dialysis patients regularly receiving LMWHs or APtDs, or both, show lower BMD parameters measured in the femoral neck. They therefore require more frequent monitoring of BMD in this region and timely prophylaxis against osteoporosis.

TABLE II Values of T score in the study patients taking (group I) or not taking (group II) anticoagulants

T Score	Femoral neck		Lumbar spine L2–L4	
	I	II	I	II
More than –1.0	0	12	5	9
More than –2.5 and less than –1.0	8	3	5	7
Less than –2.5	6	1	4	0

TABLE III Parameters that were not significantly different ($p > 0.05$) in the study patients taking (group I) or not taking (group II) anticoagulants

Parameter	Group I	Group II
BMD, L2-L4 (g/cm ²)	1.023±0.299	1.120±0.222
T Score (L2-L4)	-1.67 (-3.95 to 4.07)	-0.52 (-2.09 to 2.67)
BMD, L2-L4, as % YA	80.4 (60.4 to 139.0)	94.0 (71.3 to 127.0)
Z Score, L2-L4	-0.94 (-4.41 to 4.49)	0.12 (-1.65 to 2.33)
BMD, L2-L4, as % AM	89.0 (59.0 to 145.0)	101.0 (73.2 to 134.0)
Parathormone (pg/mL)	201.5 (31.7 to 913.0)	212.5 (12.3 to 1967.0)
Alkaline phosphatase (IU/L)	78.9±21.7	87.3±43.3
Total calcium (mg/dL)	8.6±0.9	9.2±0.8
Phosphates (mg/dL)	5.3±1.0	5.4±1.6
Blood pH	7.39 (7.30 to 7.46)	7.36 (7.30 to 7.45)
Hemoglobin (g/dL)	11.4±1.4	11.5±0.9
WBCs (G/L)	6.7±1.8	7.6±2.1
Platelets (G/L)	225±75	243±64
Mean corpuscular volume (fL)	89.9±16.0	94.3±4.8
CRP (mg/L)	1.08 (0.00 to 31.30)	1.15 (0.00 to 12.20)
Cholesterol (mg/dL)	210±37	210±54
Waist circumference (cm)	97.0 (71.0 to 121.0)	94.5 (70.5 to 119.0)
Hip circumference (cm)	103.0 (82.0 to 130.0)	103.2 (80.5 to 115.5)
Body mass index (kg/m ²)	25.9 (18.9 to 41.5)	25.9 (17.9 to 38.4)
Lean body mass (kg)	50.15±11.83	49.86±9.19
Total body water (L)	39.6±8.3	37.1±6.9
TBW% TBM	54.6±5.6	51.8±6.4
ECW% TBM	45.6±6.2	43.3±2.7

BMD = bone mineral density; YA = young adults; AM = age matched; WBCs = white blood cells; CRP = C-reactive protein; TBW = total body water; TBM = total body mass; ECW = extracellular water.

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