Bone Disease and Serum Fibroblast Growth Factor-23 Levels in Renal Transplant Recipients

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ABSTRACT

Background. Posttransplantation bone disease develops commonly and results in important complications. In this study, we aimed to investigate the relationship between bone diseases and serum fibroblast growth factor-23 (FGF-23) in renal transplant recipients.

Methods. This study was conducted in 106 kidney transplant recipients (KTrs; group G1) and 30 patients with chronic kidney disease (group G2). Patients with fever, heart failure, angina pectoris, acute renal failure, malignant disease, or any gastrointestinal disease were excluded. KTrs were treated with triple immunosuppressive drugs including glucocorticoids. Complete blood count (CBC), blood urea nitrogen (BUN), creatinine, glomerular filtration rate (GFR, Modification of Diet in Renal Disease [MDRD] formula), lipid profile, calcium (Ca), phosphorous (P), parathormone (PTH), 25OHD3, serum levels of tacrolimus/cyclosporine, and intact FGF-23 were measured. Bone mineral density (BMD) was measured with dual energy X-ray absorptiometry.

Results. The mean patient age was 40.1 ± 11.1 years and 39.2 ± 11.3 years in G1 and G2, respectively ($P > .05$). In G1 and G2, 76 and 15 patients were male, respectively. Compared with the G2 patients, G1 patients had lower body mass index (BMI), serum glucose levels, P, Mg, and Ca·P ($P < .05$ for all). T scores of the lumbar vertebrae/femur were -1.82 ± 0.99/-1.34 ± 0.89 and -1.13 ± 1.34/-0.51 ± 1.18 in G1 and G2 patients, respectively ($P < .05$ for all). The incidences of osteopenia/osteoporosis in the lumbar spine and femur were 50.9%/27.4% and 57.5%/10.4% in G1 and 16.6%/23.3%, and 40%/3.3% in G2. There were positive correlations between BMD and BMI, the time elapsed after renal transplantation, and GFR. In our study, a statistically significant relationship was found between lipid parameters and BMD, PTH, and 250HD3 levels, as well as use of corticosteroid and calcineurin inhibitors ($P < .05$ for all). In G1 and G2, BMD of the lumbar spine in patients with serum creatinine >1.5 mg/dL was lower than that in patients with serum creatinine <1.5 mg/dL.

Conclusion. The association between age and BMD was found only in the femur of KTrs. No relationship was observed between serum FGF-23 levels and BMD values. In both groups, the BMD T score of the lumbar spine was lower compared to the BMD T score of the femur and in patients with serum creatinine >1.5 mg/dL. In long-term follow-up of renal transplantation by as much as 58 months, the incidence of bone disease such as osteoporosis/osteopenia was as high as 67% and was also higher than that of nontransplant patients with similar GFR. In addition to decreased renal function, dyslipidemia, inflammation, and continuing hypophosphatemia were also accompanied by decreased BMD as in cardiovascular disease in KTrs.

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A SUCCESSFUL kidney transplantion increases the quality of life of a patient with chronic renal failure, and offers a significant reduction in mortality compared to that in patients undergoing chronic dialysis treatment [1]. However, posttransplantation osteopenia and/or osteoporosis can increase the risk of bone fractures [2–4]. Various factors such as immunosuppressive drugs (especially corticosteroids), diabetes mellitus, persistent hyperparathyroidism, vitamin D deficiency, and loss of graft function are risk factors for post−renal transplantation bone disease [5–7].

Fibroblast growth factor-23 (FGF-23) increases urinary phosphate excretion and inhibits calcitriol synthesis. FGF-23 has a direct impact on the parathyroid gland, reducing parathyroid hormone (PTH) secretion [8]. Increased production of FGF-23 continues for the first 3 months posttransplantation. Corticosteroids, calcineurin inhibitors, and sirolimus stimulate FGF-23 production [9]. During this period, phosphate supplementation for hypophosphatemia and active vitamin D3 therapy may have an FGF-23−boosting impact [10]. Currently it is considered that posttransplantation osteoporosis may be associated with the phosphaturic effect of FGF-23, and thus existing hypophosphatemia and the negative impact of FGF-23 on bone mineralization independent of phosphate values [11]. In this study, we aimed to investigate the relationship between bone diseases and FGF-23 in kidney transplant recipients.

METHODS

Patients

In this study, 106 renal transplant recipients (KTrs) (group G1) and 30 patients with chronic kidney disease (CKD) and similar glomerular filtration rates (GFR) (group G2) were included. The exclusion criteria were malignant disease, clinically overt heart disease, liver disease, infectious disease, cerebrovascular accident, or history of surgery except kidney transplantation in the past 6 months. Patient characteristics and results of blood and urine tests were recorded. Blood tests were white blood cell (WBC), hematocrit (Hct), platelets, fasting blood glucose (Glu), blood urea nitrogen (BUN), creatinine (Cre), uric acid (UA), total protein, albumin (Alb), alkaline phosphatase (ALP), aspartate transaminase (AST), alanine transaminase (ALT), sodium (Na), potassium (K), calcium (Ca), phosphorus (P), magnesium (Mg), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides (TG), thyroid-stimulating hormone (TSH), vitamin B12 (VI-B12), folic acid, C-reactive protein (CRP), parathyroid hormone (PTH), 25-OH vitamin D3, osteocalcin, and C-telopeptide. In 24-hour urine samples, glucose, P, Ca, Cre, K, Protein, Na, Urea, and UA were also measured. GFR was calculated with the Modification of Diet in Renal Disease (MDRD) equation.

Serum FGF-23 was measured by using Millipore Human FGF-23 intact ELISA kit, with Chromate micro-ELISA device. Bone mineral density (BMD) was evaluated by the dual energy X-ray absorptiometry (DEXA) method using a HOLOGOGIC Discovery W, USA device. The lowest value determined as a T score of the femur and lumbar vertebrae was accepted. Results were recorded in accordance with the definitions recommended by the World Health

Table 1. Clinical Characteristics and Laboratory Values of Patients

		G1 (n = 106)	G2 (n = 30)	
	Normal Reference Range	Mean ± SD	Mean ± SD	*P*
Body mass index (kg/m^2)	18.5–24.9	24.41 ± 4.08	27.308 ± 5.45903	.002
Hemodialysis duration (mo)	–	25.4 ± 37.91	–	–
CAPD duration (mo)	–	5.41 ± 17.55	–	–
Posttransplantation duration (mo)	–	58.93 ± 34.26	–	–
White blood cells (10^3 pcs/μL)	4.3–10.3	8500.6 ± 2770.9	9725 ± 3049.6	.038
Hematocrit (%)	39.5–50.3	41.7 ± 7.38	36.43 ± 5.53	<.001
Glucose (mg/dL)	70–105	91.32 ± 22.45	116.37 ± 61.8	.001
BUN (mg/dL)	5–20	17.03 ± 6.54	28.27 ± 15.66	<.001
Creatinine (mg/dL)	0.8–1.2	1.23 ± 0.39	1.71 ± 0.92	<.001
Protein (g/dL)	6.6–8.7	6.99 ± 0.6	6.42 ± 0.89	<.001
Albumin (g/dL)	3.4–4.8	4.10 ± 0.39	3.52 ± 0.68	<.001
Potassium (mmol/L)	3.5–5.1	4.09 ± 0.71	4.62 ± 0.47	<.001
Magnesium (mg/dL)	1.6–2.6	1.90 ± 0.22	2.07 ± 0.23	<.001
Calcium (mg/dL)	8.4–9.7	9.57 ± 0.59	9.14 ± 0.58	.001
Phosphorus (mg/dL)	2.7–4.5	3.02 ± 0.58	3.69 ± 0.71	<.001
CaXP	<55	28.77 ± 5.34	33.5 ± 6.48	<.001
C-telopeptide (ng/mL)	0.01–0.584	0.611 ± 0.32	0.758 ± 0.42	.039
Osteocalcin (ng/mL)	0–26.3	36.59 ± 23.84	39.92 ± 30.48	.527
Parathormone (pg/mL)	12–88	127.41 ± 131.74	106.18 ± 107.039	.419
CRP (mg/dL)	0–0.08	0.77 ± 1.32	1.38 ± 2.81	.093
25OHD3 (ng/mL)	10–60	20.52 ± 12.86	19.64 ± 10.40	.731
FGF-23 (pg/mL)	–	25.29 ± 30.81	28.86 ± 26.50	.567
Lumbar spine T score	≤−1	−1.82 ± 0.99	−1.13 ± 1.34	.003
Femur T score	≤−1	−1.34 ± 0.89	−0.51 ± 1.18	<.001
GFR (MDRD) (mL/min)	–	72.56 ± 27.055	65.19 ± 54.60	.308

Abbreviations: CAPD, continous ambulatory peritoneal dialysis; BUN, blood urea nitrogen; CRP, C-reactive protein; FGF-23, fibroblast growth factor-23; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.