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Fibroblast Growth Factor–23 Levels Are Associated With Uric Acid But Not Carotid Intima Media Thickness in Renal Transplant Recipients

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ABSTRACT

Introduction. Cardiovascular disease (CVD) is the leading cause of mortality in chronic kidney disease (CKD) patients. Fibroblast growth factor–23 (FGF-23) is associated with atherosclerosis and cardiovascular mortality in CKD patients and healthy subjects. However, data in renal transplant recipients (RTR) are scarce. We aimed to determine factors associated with FGF-23 and to explore its relationship to atherosclerosis.

Methods. Forty-six patients and 44 controls were included. FGF-23 was measured from plasma. Carotid intima media thickness (CIMT) was evaluated ultrasonographically.

Results. Patients had higher waist circumference (WC; 92.2 ± 14.9 vs 85.3 ± 11.0 cm; $P < .05$), glucose (99.8 ± 17.2 vs 90.3 ± 6.5 mg/dL; $P < .01$), creatinine (1.43 ± 0.6 vs 0.86 ± 0.1 mg/dL; $P < .01$), triglyceride (160.4 ± 58.9 vs 135.6 ± 59.8 mg/dL; $P < .05$), white blood cells (WBC; 7938.6 ± 2105.2 vs 6715.7 ± 1807.5 WBC/mm^3; $P < .01$), ferritin (217.0 ± 255.8 vs 108.3 ± 142.4 ng/mL; $P < .05$), uric acid (6.5 ± 1.6 vs 4.7 ± 1.3 mg/dL; $P < .01$), C-reactive protein (CRP; 8.2 ± 18.2 vs 5.3 ± 7.9 mg/L; $P < .01$), parathyroid hormone (PTH; 89.7 ± 59.2 vs 44.1 ± 16.7 pg/mL; $P < .01$), and alkaline phosphatase (ALP; 162.5 ± 86.6 vs 74.2 ± 21.9 U/L; $P < .01$). FGF-23 was higher in patients (11.7 ± 7.2 vs 9.6 ± 6.8 pg/mL; $P < .05$). CIMT was similar (0.58 ± 0.09 vs 0.57 ± 0.1 mm; $P > .05$). WC, creatinine, and uric acid were positively correlated with FGF-23, whereas albumin showed negative correlation. On multivariate analysis only creatinine and uric acid were determinants of FGF-23.

Conclusion. FGF-23 levels are associated with uric acid in RTR. Larger studies are needed to confirm this finding.

CARDIOVASCULAR disease (CVD) is the leading cause of morbidity and mortality in patients with chronic kidney disease (CKD), including those with kidney transplantation. It accounts for more than 50% of deaths, even in patients with functioning renal grafts [1,2]. Because traditional risk factors are insufficient to explain the increased cardiovascular event rate in this patient population, nontraditional risk factors, such as abnormal mineral metabolism, have been postulated as potential factors [3]. Several studies have consistently demonstrated altered mineral metabolism to be associated with atherosclerosis in patients with CKD [3]. However, data on the relationship between bone mineral disorders and atherosclerosis in renal transplant recipients (RTR) is scarce.

Fibroblast growth factor–23 (FGF-23) is a hormone produced mainly by osteocytes that regulates phosphate metabolism. FGF-23 exerts its biological effects through FGF receptors in a Klotho-dependent manner [4]. It induces phosphaturia by suppression of the Na/P cotransporters in the proximal tubules and decreases calcitriol levels [4]. Recently, several studies have shown FGF-23 levels to be associated with impaired vasoreactivity, increased arterial stiffness, left ventricular hypertrophy, cardiovascular mortality, and atherosclerosis in both hemodialysis patients and healthy subjects [5–8]. However, little is known about the relationship between atherosclerosis and FGF-23 levels in RTR. The aims of the present study were to determine the

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factors associated with FGF-23 levels and to explore the relationship between atherosclerosis as assessed based on carotid intima media thickness (CIMT) and FGF-23 levels in RTR.

SUBJECTS AND METHODS

Patients

The study was approved by the Ethics Committee of Marmara University Medical School and was carried out in accordance with the declaration of Helsinki. All subjects gave informed consent for participation. Forty-six patients with stable allograft function who had received a renal transplant at least 6 months previously and 44 age- and gender-matched healthy controls were included in the study. Stable allograft function was defined by no change in serum creatinine level >0.2 mg/dL within the 6 months prior to the study. Patients with malignancy, infectious or noninfectious inflammatory disease, history of a rejection episode within the preceding 6 months, multiple-organ transplantation, and those younger than 18 years were excluded from the study. Primary diseases were chronic glomerulonephritis in 5 patients (10.9%), diabetes in 4 patients (8.7%), hypertension in 4 patients (8.7%), polycystic kidney disease in 4 patients (8.7%), amyloidosis caused by familial Mediterranean fever in 3 patients (6.5%), interstitial nephritis in 2 patients (4.3%), vesico-ureteral reflux in 2 patients (4.3%), and unknown in 22 patients (47.8%).

At a routine transplantation clinic visit, a brief history and physical examination were performed and a list of current medications, blood pressure, height, and weight were collected. Blood and urine samples were obtained at that visit for the determination of routine laboratory data. Average values for parathyroid hormone (PTH) and C-reactive protein (CRP) were calculated using 3 measurements. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2) and waist circumference (WC) was measured at the narrowest point between the 12th rib and the iliac crest.

Laboratory Measurements

Blood samples were drawn after an overnight fasting of at least 12 hours. Biochemical parameters were measured using an autoanalyzer (Olympus AU 800; Olympus Diagnostica GmhH, Hamburg, Germany). PTH levels were determined by means of chemiluminescent immunoassay (Liaison N-tact; DiaSorin Inc, Stillwater, Minn, United States) and CRP values were measured using a nephelometer (Behring BN II; Dade Behring, Deerfield, Ill, United States). Plasma FGF-23 was measured using an enzyme-linked immunosorbent assay (ELISA; Immunotopics, San Clemente, Calif, United States) that detects the intact molecule.

Measurement of CIMT

Ultrasonography of the carotid arteries was performed by an experienced and independent ultrasonographer, who was masked to all clinical data, using a 10 MHz vascular ultrasound probe (Vingmed Ultrasound, System 5, Horten, Norway). CIMT was defined as a low-level echo gray band that does not project into the arterial lumen and is the distance from the leading edge of the lumen-intima interface to the leading edge of the media-adventitia interface of the far edge. Three segments were measured bilaterally: the 1-cm section of the common carotid artery immediately proximal to the beginning of the dilatation of the bifurcation, the 1-cm section of the bifurcation immediately proximal to the tip of the flow divider and the 1-cm section of the internal carotid artery immediately distal to the tip of the flow divider. The mean of the 6 measurements was used as the carotid artery IMT. A plaque was defined as a focal thickening relative to the adjacent segment with a distinct area of hyperechogenicity or protrusion into the lumen of the vessel that was at least 50% thicker than the surrounding area.

Statistical Analysis

Statistical analysis was performed using SPSS for Windows, version 10.0, software (SPSS Inc, Chicago, Ill, United States). Shapiro-Wilks test of normality was used to analyze data distribution. All variables that are distributed normally are presented as mean ± standard deviation (SD); those with non-normal distribution are presented as median and range. The Student t test was used to compare means between groups and the chi-square test was used to compare proportions between groups. For correlations between variables, the Pearson test was used for normally distributed data and the Spearman test for those with nonparametric distributions. To assess the influence of tested parameters on CIMT, multiple regression analysis was performed. We considered P values less than .05 as statistically significant.

RESULTS

Forty-six RTR and 44 age- and gender-matched healthy controls were included in the study. Mean age was 41.5 ± 11.0 years. The mean transplantation time was 47.8 ± 29.0 months. Thirty patients (65.2%) underwent transplantation from a living related donor. Maintenance immunosuppression consisted of corticosteroids in 44 (95.7%) patients, calcineurin inhibitors in 44 (95.7%) patients, and an antimetabolite agent in 40 (87.0%) patients.

The demographic, clinical, and laboratory parameters of the study groups are shown in Table 1. There were no differences between the 2 groups in terms of age, gender, BMI, total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol, hemoglobin, albumin, Ca, P, and 25-OH-D vitamin levels (Table 1). Patients had higher WC (92.2 ± 14.9 vs 85.3 ± 11.0 cm; $P < .05$), glucose (99.8 ± 17.2 vs 90.3 ± 6.5 mg/dL; $P < .01$), creatinine (1.43 ± 0.6 vs 0.86 ± 0.1 mg/dL; $P < .01$), triglyceride (160.4 ± 58.9 vs 135.6 ± 59.8 mg/dL; $P < .05$), white blood cells (WBC; 7938.6 ± 2105.2 vs 6715.7 ± 1807.5 WBC/mm^3; $P < .01$), ferritin (217.0 ± 255.8 vs 108.3 ± 142.4 ng/mL; $P < .05$), uric acid (6.5 ± 1.6 vs 4.7 ± 1.3 mg/dL; $P < .01$), CRP (8.2 ± 18.2 vs 5.3 ± 7.9 mg/L; $P < .01$), PTH (89.7 ± 59.2 vs 44.1 ± 16.7 pg/mL; $P < .01$), and alkaline phosphatase (ALP; 162.5 ± 86.6 vs 74.2 ± 21.9 U/L; $P < .01$) levels as compared with healthy controls.

Even though FGF-23 levels were significantly higher in the patient group (11.7 ± 7.2 vs 9.6 ± 6.8 pg/mL; $P < .05$), CIMT values were similar in both groups (0.58 ± 0.09 vs 0.57 ± 0.1 mm; $P > .05$). Further analysis revealed that gender, dialysis modality prior to transplantation, or transplantation type (living donor vs cadaveric kidney transplantation) did not affect FGF-23 levels. On univariate analysis WC, creatinine level, and uric acid level were positively correlated with FGF-23, whereas albumin level was negatively correlated. We included age, WC, creatinine,