Fasting Long-Acting Natriuretic Peptide Correlates Inversely With Metabolic Syndrome in Kidney Transplant Patients

B.-G. Hsu, M.-H. Shih, Y.-C. Yang, G.-J. Ho, and M.-C. Lee

ABSTRACT

The metabolic syndrome (MetS) is a risk factor for posttransplant diabetes mellitus, chronic graft dysfunction, graft loss, occurrence of atherosclerotic events, and patient death among kidney transplantation patients. Long-acting natriuretic peptide (LANP) is among the peptide hormones in atrial natriuretic peptide prohormone. Low levels of natriuretic peptide may lead to reduced lipolysis and excessive weight gain in obese patients. This study was undertaken to evaluate the relationship between MetS and fasting serum LANP concentration among kidney transplanted patients. Fasting blood samples were obtained from 69 kidney recipients. The MetS and its components were defined using the diagnostic criteria of the International Diabetes Federation. Fasting LANP levels were measured using a commercial enzyme immunoassay kit. The prevalence rate of MetS was 20.3% (14/69). Fasting LANP level negatively correlated with MetS among these patients ($P = .010$). Using univariate linear regression analysis, serum LANP values were negatively correlated with hemoglobin ($r = -0.252$; $P = .037$), and positively correlated with blood urea nitrogen ($r = 0.254$; $P = .035$) and creatinine ($r = 0.311$; $P = .009$). Multivariate forward stepwise linear regression analysis of the significant variables revealed that creatinine (R^2 change = 0.097; $P = .009$) was an independent predictor of fasting serum LANP concentration among kidney transplanted patients. Serum LANP concentration correlates inversely with MetS; for these patients, creatinine is an independent predictor of the serum LANP value.

WITHIN THE 126-amino acid atrial natriuretic peptides (ANP) prohormone are 4 peptide hormones: Long-acting natriuretic peptide (LANP; *N*-terminal pro-ANP 1–30), vessel dilator (*N*-terminal pro-ANP 31–67), kaliuretic peptide (*N*-terminal pro-ANP 79–98), and ANP (*N*-terminal pro-ANP 99–126). These peptide hormones have significant diuretic, natriuretic, and blood pressure-lowering properties in animals and humans.[1] The biologic effects of ANP prohormone include vasodilation mediated via enhancing guanylate cyclase activity, with a resultant increase in the intracellular messenger cyclic guanosine monophosphate (cGMP), and inhibit the vasoconstrictive peptide endothelin.[2] Natriuretic peptides are also potent lipolytic agents that act in adipose tissue.[3] ANP activates cGMP-dependent protein kinase, leading to perilipin and hormone-sensitive lipase phosphorylation, and induces lipolysis.[4]

The metabolic syndrome (MetS) is a risk factor for posttransplant diabetes mellitus, chronic graft dysfunction, graft loss, occurrence of atherosclerotic events, and patient death in kidney transplantation patients.[5,6] Obese patients have reduced plasma levels of natriuretic peptides.[3] Obese individuals in the cohorts of the Framingham Heart Study were found to hold considerably lower plasma *N*-terminal proatrial natriuretic peptide levels than those of normal weight.[7] Lower plasma *N*-terminal proatrial natriuretic peptide levels were also associated with the development of the MetS.[8] There is no study about the association between serum LANP levels and MetS in kidney transplanted patients. The aim of this study was to investigate the relation-

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ship between the fasting serum LANP level and the MetS among kidney transplant recipients.

MATERIALS AND METHODS

Patients

Sixty-nine renal transplant recipients were studied in April 2010 in a medical center in Hualien, Taiwan. This group was composed of 41 men and 24 women, and the subjects ranged in age from 31 to 73 years. The study was approved by the Protection of Human Subjects Institutional Review Board of Tzu-Chi University and Hospital. Patients were excluded if they had any acute infection, malignancy, acute rejection, acute myocardial infarction, pulmonary edema, or heart failure at the time of blood sampling. If a patient refused to provide informed consent for the study, they were also excluded.

Anthropometric Analysis

Body weight was measured to the nearest half kilogram with the patient in light clothing and without shoes. Height was measured to the nearest half centimeter. Waist circumference was measured to the nearest half centimeter at the shortest point below the lower rib margin and the iliac crest. Body mass index (BMI) was calculated as weight (kilograms) divided by height squared (meters). Bioimpedance measurements of fat mass were performed at the bedside according to the standard, tetrapolar, whole-body (hand–foot) technique, using a single-frequency (50-kHz) analyzer (Biodynamic-450, Biodynamics Corporation, Seattle, Wash). Measurements were performed by the same operator; fat mass data were collected and analyzed by specific formulae offered by the manufacturer.[9,10]

Biochemical Determinations

Fasting blood samples of approximately 0.5 mL for measuring complete blood count (Sysmex K-1000, Bohemia, NY) and other factors were immediately centrifuged at 3000 *g* for 10 minutes. Serum samples were stored at 4°C and used for biochemical analyses within 1 hour of collection. Serum levels of blood urea nitrogen (BUN), creatinine (Cre), fasting glucose, total cholesterol, triglyceride (TG), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), albumin, globulin, glutamic oxaloacetic transaminase, and glutamic pyruvic transaminase were measured using an autoanalyzer (COBAS Integra 800, Roche Diagnostics, Basel, Switzerland). Serum LANP [pre-proANP (26–55); Phoenix Pharmaceuticals Inc., Burlingame, Calif], levels were measured using a commercial available enzyme immunoassay kit.[9,10] The limit of detection calculated as the concentration of human LANP corresponding with the blank average minus 3 standard deviations was 0.1 ng/mL. The inter- and intra-assay coefficients of variation for LANP were 6.2% and 5.4%, respectively. Serum intact parathyroid hormone (Diagnostic Systems Laboratories, Webster, Tex) levels were measured using a commercially available enzyme-linked immunosorbent assay.[9,10]

The MetS and Its Components

The presence of the MetS was established using the International Diabetes Federation definition.[11] Patients were concluded to have the MetS if they exhibited central (abdominal) obesity with a waist circumference of ≥90 cm (Chinese males) or ≥80 cm (Chinese females), plus ≥2 of the following: (1) Fasting serum glucose values of ≥110 mg/dL; (2) TG values of ≥150 mg/dL; (3) HDL-C concentrations <40 mg/dL for males or <50 mg/dL for females; and (4) blood pressure measurements of ≥130/85 mm Hg or use of antihypertensive agents. The presence of type 2 diabetes was established according to World Health Organization criteria.[12] A patient was considered diabetic if he or she exhibited an FPG value of ≥126 mg/dL, if his or her 2-hour glucose value during an oral glucose tolerance test was ≥200 mg/dL, or if antidiabetic therapy (oral agent or insulin) was required.

Statistical Analysis

Data are expressed as mean values ± standard deviation (SD) and were tested for normal distribution by Kolmogorov–Smirnov statistics. Comparisons between patients were performed using the Student's independent *t* test (2 tailed) for normally distributed data or the Mann–Whitney *U* test for parameters that presented with non-normal distribution (fasting glucose, BUN, LANP). Clinical variables that correlated with LANP in kidney transplanted patients were evaluated by univariate linear regression analyses. Variables significantly associated with LANP in these patients were tested for independence by multivariate forward stepwise regression analysis. Data were analyzed using SPSS for Windows (version 13.0; SPSS Inc., Chicago, Ill). $P < .05$ was considered significant.

RESULTS

Demographic, biochemical, and clinical characteristics of the 69 KT patients are presented in Tables 1 and 2. Comorbid conditions included diabetes ($n = 12$; 17.4%) and hypertension ($n = 37$; 53.6%). Prescribed therapeutic agents included tacrolimus ($n = 53$; 76.8%), mycophenolate mofetil ($n = 25$; 36.2%), myfortic ($n = 40$; 58.0%), steroids ($n = 67$; 97.1%), rapamycin ($n = 3$; 4.3%), and cyclosporine ($n = 14$; 20.3%).

Clinical characteristics and fasting serum LANP values for the 69 patients are presented in Table 2. LANP level negatively correlated with MetS among kidney transplanted patients ($P = .010$). No significant differences in LANP values were found as a function of gender; presence of diabetes or hypertension; transplantation model; or use of tacrolimus, mycophenolate mofetil, myfortic, steroid, rapamycin, or cyclosporine.

Univariate linear analysis of clinical variables associated with fasting serum LANP concentrations is presented in Table 3 Hemoglobin ($r = -0.252$; $P = .037$) was negatively correlated, whereas BUN ($r = 0.254$; $P = .035$) and Cre ($r = 0.311$; $P = .009$) were positively correlated with serum LANP values. Multivariate forward stepwise linear regression analysis of the variables significantly associated with fasting serum LANP values revealed that Cre (R^2 change = 0.097; $P = .009$) was independent predictors of these values for KT patients (data not shown).

DISCUSSION

The findings of this study reveal that, for renal transplant recipients, fasting LANP concentrations correlate inversely with the MetS. Serum Cre was found to be independent predictor of the fasting serum LANP concentration among these patients.