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Original Article

Serum osteoprotegerin levels associated with the aortic augmentation index in renal transplant recipients

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ABSTRACT

Objectives: Arterial stiffness is recognized as an independent risk factor for cardiovascular morbidity and mortality. Recent studies found that osteoprotegerin (OPG) is associated with arterial stiffness and may reflect endothelial dysfunction. The aim of this study was to evaluate the relationship between fasting serum OPG levels and the aortic augmentation index (AIx) in renal transplant recipients.

Materials and methods: Fasting blood samples were obtained from 66 renal transplant recipients. The aortic AIx was measured using a validated tonometry system (SphygmoCor). Serum OPG levels were measured using a commercial enzyme-linked immunosorbent assay kit.

Results: Univariate linear analysis of the aortic AIx in renal transplant recipients revealed that body fat mass ($r = 0.377$, $p = 0.002$), aortic diastolic blood pressure (DBP; $r = 0.307$, $p = 0.020$), triglycerides ($r = 0.260$, $p = 0.035$), and logarithmically transformed OPG (log-OPG, $r = 0.402$, $p < 0.001$) were positively correlated, whereas height ($r = 0.361$, $p = 0.004$) and body weight ($r = 0.212$, $p = 0.041$) were negatively correlated with the aortic AIx in renal transplant recipients. Multivariate forward stepwise linear regression analysis of the factors significantly associated with the aortic AIx showed that log-OPG ($R^2 = 0.213$, $p < 0.001$), height ($R^2 = 0.081$, $p = 0.009$), and aortic DBP ($R^2 = 0.058$, $p = 0.022$) were independent predictors of the aortic AIx in renal transplant recipients.

Conclusion: These results suggest that the serum fasting OPG level is associated with the aortic AIx in renal transplant recipients.

1. Introduction

Cardiovascular (CV) disease is still a major cause of mortality in renal transplant recipients. This is partially attributed to nonclassic CV disease risk factors including arterial stiffness, an established independent predictor of mortality in several patient populations [1]. The European Society of Cardiology Working Group described the importance of peripheral noninvasive vascular biomarkers for primary and secondary CV disease prevention [2]. Among them, noninvasive methods to assess central hemodynamics/wave reflections such as the aortic augmentation index (AIx) of central blood pressure have been widely used as clinical indices of arterial stiffness [2,3]. The AIx (augmentation pressure-to-pulse pressure ratio) is a measure of the contribution that wave reflection makes to the central pressure wave: it is defined as the difference between the second and first peaks corresponding to the systolic blood pressure (SBP) and expressed as a percentage of the pulse pressure. Thus, the AIx is an indirect measure of central arterial stiffness, but mainly a direct measure of central wave reflection [4].

Vascular calcification is a tightly controlled process similar to bone formation, where mineralization of the internal elastic lamina and elastic fibers in the media results in vascular stiffening [5–7].

Conflicts of interest: none.

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Osteoprotegerin (OPG) is considered a vascular calcification inhibitor. It can prevent vascular calcification by blocking the bone remodeling process in vascular tissue and by neutralizing the proapoptotic actions of tumor necrosis factor–related apoptosis-inducing ligand [6]. Elevated serum OPG is an independent predictor of death from any cause or of CV death among renal transplant recipients [8]. In the Assessment of Lescol in Renal Transplantation study, elevated serum OPG level was also found to be independently associated with renal events, CV events, and mortality in renal transplant recipients [9]. Our previous studies noted that high OPG levels were associated with central arterial stiffness measured by carotid–femoral pulse wave velocity in hypertensive patients and renal transplant recipients [10,11]. The aim of this study was to determine the relationship between fasting serum OPG levels and arterial stiffness, as measured by the aortic AIx, in renal transplant recipients.

2. Materials and methods

2.1. Patients

Between May and August 2013, 66 renal transplant recipients from a medical center in Hualien, Taiwan, were enrolled in this study. The Human Subjects Institutional Review Board of Tzu Chi University and General Hospital approved this study. Patients were excluded if they had any acute infection, malignancy, acute rejection, acute myocardial infarction, or pulmonary edema at the time of blood sampling as well as if they had an arterial–venous shunt or had received a graft in the hands. Patients using medications related to calcium, active vitamin D metabolites, bisphosphonates, teriparatide, or estrogen were excluded as were those who refused to provide informed consent.

2.2. Anthropometric analysis

The participants' weights were measured in light clothing and without shoes to the nearest 0.5 kg, and their height was measured to the nearest 0.5 cm. Body mass index was calculated as the weight in kilogram divided by the height in meter square [10–12]. 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, WA, USA). Measurements were carried out by the same operator for all patients.

2.3. Biochemical investigations

Fasting blood samples (approx. 5 mL collected) of approximately 0.5 mL for hemoglobin and white blood cell counts (Sysmex K-1000, Sysmex American, Mundelein, IL, USA) were immediately centrifuged at 3000*g* for 10 minutes. Serum levels of blood urea nitrogen (BUN), creatinine (Cre), fasting glucose, total cholesterol, triglycerides (TGs), high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, total calcium, and phosphorus were measured using an autoanalyzer (cobas integra 800, Roche Diagnostics, Basel, Switzerland) [10–12]. Serum OPG levels (eBioscience Inc., San Diego, CA, USA) were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) [10–12]. The limit of detection calculated as the concentration of human OPG corresponding to the blank average minus three standard deviations was 2.5 pg/mL. The inter- and intra-assay coefficients of variation for OPG were 8.0% and 7.0%, respectively. The participants' serum intact parathyroid hormone (iPTH; Diagnostic Systems Laboratories, Webster, TX, USA) levels were measured using a commercially available ELISA [10–12]. The equation from the Modification of Diet in Renal Disease was used to calculate the estimated glomerular filtration rate in this study.

2.4. Pulse wave analysis and aortic AIx assessment

Patients were positioned supine and allowed to rest for 10 minutes prior to the test. Consumption of food, drink, alcohol, and tobacco was not restricted, but patients were not allowed to sleep or talk during the testing procedure. Pulse wave analysis was performed by applanation tonometry on the right radial artery and analyzed by SphygmoCor software (SphygmoCor system, AtCor Medical, West Ryde, Australia) [10,11]. This software calculates a number of major indices including the aortic AIx aortic SBP, and aortic diastolic blood pressure (DBP). Pulse pressure was calculated by subtracting the DBP from the SBP.

2.5. Statistical analysis

Data were tested for normal distribution using the Kolmogorov–Smirnov test. Data were expressed as means ± standard deviation for normally distributed data and as medians and interquartile ranges for non-normally distributed data. The glucose, BUN, Cre, iPTH, and OPG datasets showed skewed non-normal distributions, and therefore, were recalculated by transformation to the logarithm base 10; after this transformation, the log-glucose, log-BUN, log-Cre, log-iPTH, and log-OPG were normally distributed. Clinical variables that correlated with the aortic AIx values in renal transplant recipients were first evaluated by univariate linear regression analysis. Variables that were significantly associated with the aortic AIx in the renal transplant recipients were tested for independence by multivariate forward stepwise regression analysis. All data were analyzed using SPSS for Windows (version 19.0; SPSS Inc., Chicago, IL, USA). A p value of less than 0.05 was considered statistically significant.

3. Results

The clinical and laboratory anthropometric and biochemical data of the 66 renal transplant recipients are presented in Table 1. Table 2 shows that 40 patients had diabetes (60.6%) and 17 had hypertension (25.8%). The immunological medications prescribed to the renal transplant recipients included tacrolimus (n = 38, 57.6%), mycophenolate mofetil or mycophenolic acid (n = 49, 74.2%), steroids (n = 54, 81.8%), rapamycin (n = 11, 16.7%), and cyclosporine (n = 17, 25.8%). There were no statistically significant differences in aortic AIx values based on sex, transplantation model, diabetes, hypertension, or use of the immunological medications listed.

Univariate linear analysis of the aortic AIx values of the 66 renal transplant recipients is presented in Table 3. Body fat mass (r = 0.377, p = 0.002), aortic DBP (r = 0.307, p = 0.020), TGs (r = 0.260, p = 0.035), and log-OPG (r = 0.402, p < 0.001) were positively correlated, whereas height (r = 0.361, p = 0.004) and body weight (r = 0.212, p = 0.041) were negatively correlated with the aortic AIx in these patients.

Multivariate forward stepwise linear regression analysis of the variables that were significantly associated with the aortic AIx levels in univariate analysis showed that log-OPG (β = 0.397, R^2 = 0.213, p < 0.001), height (β = −0.260, R^2 = 0.081, p = 0.009), and aortic DBP (β = 0.243, R^2 = 0.058, p = 0.022) were independent predictors of the aortic AIx in these patients (Table 4).