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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).

Table 1
Clinical and analytical characteristics of the 66 renal transplant recipients.

Items	Parameter	
Anthropometric data	Age (years)	51.59 ± 9.32
	KT duration (months)	71.30 ± 43.55
	Height (cm)	162.32 ± 8.36
	Body weight (kg)	62.36 ± 12.65
	Body mass index (kg/m^2)	23.78 ± 4.19
	Waist circumference (cm)	84.88 ± 11.20
	Body fat mass (%)	29.06 ± 6.39
	Aortic SBP (mmHg)	139.48 ± 16.51
	Aortic DBP (mmHg)	87.24 ± 10.57
	Pulse pressure (mmHg)	52.24 ± 12.69
	Augmentation index (%)	18.17 ± 11.09
Biochemical data	White blood count (×1000/μL)	7.02 ± 2.46
	Hemoglobin (g/dL)	12.32 ± 2.29
	Total cholesterol (mg/dL)	195.94 ± 46.83
	Triglyceride (mg/dL)	144.13 ± 108.62
	HDL-C (mg/dL)	52.27 ± 16.42
	LDL-C (mg/dL)	106.60 ± 34.45
	Fasting glucose (mg/dL)	94.50 (86.00–110.00)
	Blood urea nitrogen (mg/dL)	22.00 (17.00–34.25)
	Creatinine (mg/dL)	1.50 (1.18–2.03)
	GFR (ml/min)	43.38 ± 21.49
	Total Calcium (mg/dL)	9.21 ± 1.06
	Phosphorus (mg/dL)	3.36 ± 0.80
	Calcium-phosphorous product	30.61 ± 6.46
	iPTH (pg/mL)	115.75 (70.80–155.65)
	Osteoprotegerin (pg/L)	3.20 (1.27–9.57)

Values for continuous variables given as means ± standard deviation and variables not normally distributed given as medians and interquartile range.
DBP = diastolic blood pressure; GFR = glomerular filtration rate; HDL-C = high-density lipoprotein-cholesterol; iPTH = intact parathyroid hormone; KT = kidney transplantation; LDL-C = low-density lipoprotein-cholesterol; SBP = systolic blood pressure.

4. Discussion

The current results reveal that body fat mass, aortic DBP, TGs, and log-OPG were positively correlated, whereas height and body weight were negatively correlated with the aortic AIx in renal transplant recipients in univariate analysis. After adjusting these significant variables using multivariate forward stepwise linear regression analysis, log-OPG, height, and aortic DBP were identified as independent predictors of aortic AIx values in renal transplant recipients. A high serum OPG level was associated with the aortic AIx in renal transplant recipients.

Aortic stiffness increases central systolic pressure (increased cardiac load and oxygen consumption), lowers diastolic pressure (decreased myocardial perfusion pressure), and promotes degeneration of the elastic components of the arterial wall. The net result is an imbalance toward myocardial ischemia and an impairment of left ventricular function [2]. Aortic stiffness is a strong predictor of future CV events and all-cause mortality in humans [13]. In addition, aortic stiffness is also a strong predictor of future CV events in renal transplant recipients [14]. In a meta-analysis of 5648 patients, the aortic AIx was an independent predictor of CV events; of interest, it also independently predicted all-cause mortality [15]. Aging of the arterial system is accompanied by progressive structural changes, involving fragmentation and degeneration of elastin, increases in collagen, thickening of the arterial wall, endothelium damage, and progressive dilation of the arteries [16]. The aortic AIx was significantly higher in women than in men and the increase in AIx with age was curvilinear in a population study based on 4561 participants from the Copenhagen City Heart Study in Denmark [17]. The same group also noted that the aortic AIx directly

Table 2
Clinical characteristics and aortic augmentation index levels of the 66 renal transplant recipients.

Characteristic	*n* (%)	Augmentation index (%)	*p*
Sex			
Male	36 (54.5)	15.57 ± 11.20	0.052
Female	30 (45.5)	21.07 ± 10.41	
Diabetes			
No	26 (39.4)	15.31 ± 9.44	0.091
Yes	40 (60.6)	20.03 ± 11.78	
Hypertension			
No	49 (74.2)	17.88 ± 11.49	0.722
Yes	17 (25.8)	19.00 ± 10.13	
Transplantation model			
Cadaveric	57 (86.4)	17.44 ± 11.47	0.182
Living	9 (13.6)	22.78 ± 7.07	
Tacrolimus use			
No	28 (42.4)	17.18 ± 10.06	0.538
Yes	38 (57.6)	18.89 ± 11.87	
Mycophenolate mofetil or mycophenolic acid use			
No	17 (25.8)	19.65 ± 12.14	0.527
Yes	49 (74.2)	17.65 ± 10.79	
Steroid use			
No	12 (18.2)	19.92 ± 12.47	0.550
Yes	54 (81.8)	17.78 ± 10.85	
Rapamycin use			
No	55 (83.3)	18.31 ± 11.28	0.818
Yes	11 (16.7)	17.45 ± 10.58	
Cyclosporine use			
No	49 (74.2)	18.53 ± 11.52	0.654
Yes	17 (25.8)	17.12 ± 9.99	

* $p < 0.05$ was considered statistically significant after the Student independent *t* test.

Table 3
Correlation of aortic augmentation index levels and clinical variables by univariate linear regression analysis among the 66 renal transplant recipients.

Variable	*r*	*p*
Age (y)	0.021	0.868
Kidney transplantation duration (mo)	0.093	0.456
Height (cm)	−0.361	0.003 *
Body weight (kg)	−0.252	0.041 *
Body mass index (kg/m^2)	−0.155	0.215
Body fat mass (%)	0.377	0.002 *
Aortic systolic blood pressure (mmHg)	0.160	0.200
Aortic diastolic blood pressure (mmHg)	0.307	0.020 *
Pulse pressure (mmHg)	−0.048	0.704
White blood count (× 1000/μL)	0.002	0.987
Hemoglobin (g/dL)	−0.144	0.247
Total cholesterol (mg/dL)	0.157	0.209
Triglyceride (mg/dL)	0.260	0.035 *
HDL-C (mg/dL)	−0.049	0.698
LDL-C (mg/dL)	−0.035	0.781
Log-glucose (mg/dL)	−0.014	0.912
Log-blood urea nitrogen (mg/dL)	0.141	0.260
Log-creatinine (mg/dL)	0.006	0.962
Glomerular filtration rate (mL/min)	−0.239	0.054
Total calcium (mg/dL)	−0.115	0.356
Phosphorus (mg/dL)	0.175	0.160
Ca × P product (mg^2/dL^2)	0.118	0.347
Log-osteoprotegerin (pg/L)	0.462	<0.001 *
Log-intact parathyroid hormone (pg/mL)	0.008	0.950

* $p < 0.05$ is considered statistically significant in the univariate linear analyses.
HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol.

Table 4
Multivariate stepwise linear regression analysis of body fat mass, aortic diastolic blood pressure, triglyceride, height, body weight, and log-OPG: correlation with aortic augmentation index levels among 66 renal transplant recipients.

Variable	Beta	R^2	R^2 change	*p*
Log-osteoprotegerin (pg/L)	0.397	0.213	0.213	<0.001 *
Height (cm)	−0.260	0.294	0.081	0.009 *
Aortic diastolic blood pressure (mmHg)	0.243	0.352	0.058	0.022 *

* $p < 0.05$ is considered statistically significant in the multivariate stepwise linear regression analysis.
OPG = osteoprotegerin.

increased with height and SBP in a study based on 3432 participants [18]. However, a recent study noted that age and SBP were not significantly associated with the aortic Aix in renal transplant recipients [19]. The aortic AIx was inversely associated with height in a study on randomly selected community-dwelling adults ($N = 1152$) [20]. In normal-weight individuals, it was significantly higher in those with metabolic syndrome than in those without the syndrome [21]. Weight loss on a 12-week training program was significantly and independently associated with reduction in AIx values after adjustment for heart rate at 75 beats per minute among Japanese elderly persons [22]. Our study showed that body fat mass, aortic DBP, and TGs were positively correlated, whereas height and body weight were negatively correlated with aortic AIx in renal transplant recipients. However, our study did not find a statistically significant association between aortic AIx values and age in renal transplant recipients. There is a tendency for female renal transplant recipients to have higher aortic AIx values than men, but it just missed statistical significance in our study ($p = 0.052$). Aortic DBP was positively associated with aortic AIx, whereas height was negatively associated with aortic AIx values among renal transplant recipients in our study after multivariable analysis.

OPG is a vascular calcification inhibitor that strongly inhibits bone resorption [6]. Vascular calcification is an active, complex process that involves numerous mechanisms responsible for calcium deposition in the arterial walls, leading to an increase in arterial stiffness [7,23]. Clinical studies have suggested that an increase in serum OPG levels is associated with renal events, CV events, and mortality in renal transplant recipients [8,9]. A high level of OPG has been significantly associated with the progression of abdominal aortic calcification in renal transplant recipients [24]. The serum OPG level was also positively associated with AIx values in postmenopausal women with osteoporosis [25]. Our study showed that serum log-OPG concentrations were positively correlated with aortic AIx values in renal transplant recipients. This relationship remained significant even after adjustment for several confounders affecting renal transplant recipients.

Our study had some limitations. First, the number of patients enrolled was small, thereby weakening the statistical power of the results. Second, antihypertensive drugs such as β-blockers increase the aortic AIx by decreasing central to brachial amplification [26]. We did not record antihypertension regimens in this study. Further studies are needed to elucidate the causal relationship between serum OPG levels and aortic AIx values in renal transplant recipients.

In conclusion, this study showed positive associations between AIx values and log-OPG and aortic DBP, and a negative association between AIx values and height in renal transplant recipients. We feel further studies and investigations are needed to understand the effects of these factors on AIx values in renal transplant recipients.

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