Hyperleptinemia Is a Risk Factor for the Development of Central Arterial Stiffness in Kidney Transplant Patients

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ABSTRACT

Background. Arterial stiffness could cause adverse outcomes in kidney transplant (KT) patients. Leptin has a role in influencing vascular smooth muscle that may contribute to atherosclerosis. The aim of this study was to evaluate the relationship between fasting serum leptin concentration and carotid-femoral pulse wave velocity (cfPWV) in KT patients.

Materials and Methods. Fasting blood samples were obtained from 55 KT patients and 65 subjects from the outpatient department were enrolled as the control group. The cfPWV values of >10 m/s were used to define as the high arterial stiffness group and <10 m/s as the low arterial stiffness group. The predictive ability of leptin for arterial stiffness of KT was assessed using receiver operating characteristic (ROC) curve and multivariate logistic regression analyses.

Results. Kidney transplant patients had lower hemoglobin, but higher blood urea nitrogen, creatinine, total cholesterol, diastolic blood pressure, intact parathyroid hormone levels, and leptin levels than controls. Although cfPWV levels were higher in KT patients, there is no difference of cfPWV levels between KT patients and control ($P = .595$). Fifteen KT patients (27.3%) were defined in the high arterial stiffness group, and serum leptin level was higher in the high arterial stiffness group compared with the low arterial stiffness group in KT patients ($P < .001$). Multivariate logistic regression analysis showed that leptin (odds ratio: 1.044, 95% confidence interval [CI]: 1.016–1.072, $P = .002$) was an independent predictor of arterial stiffness in KT patients. The sensitivity, specificity, positive predictive value, negative predictive value, and area under the ROC curve predicting arterial stiffness in KT patients were 73.33%, 87.5%, 68.7%, 89.7%, and 0.828 (95% CI: 0.703–0.917, $P < .001$), and the leptin cut-off value was 74.14 ng/mL.

Conclusion. Serum fasting leptin level could predict the development of central arterial stiffness of KT patients.

CARDIOVASCULAR disease, a major cause of mortality in kidney transplant (KT) patients, is partially attributed to nonclassic cardiovascular risk factors, including arterial stiffness [1–3]. Aortic stiffness has been identified as an independent predictor of coronary events and cardiovascular mortality in hypertensive patients and in KT patients [3,4]. Hypertensive disease is followed by mechanical adaptation of the arterial wall, involving elastin fibers degradation, collagen accumulation, and reorganization of cellular elements, favoring calcium accumulation in the vascular wall and arterial stiffness [5]. On the other hand, aortic stiffness affects aortic function, reduces baroreceptor responsiveness, and increases systolic pressure, making arterial stiffness one of the causes of increased blood pressure [5]. Pulse wave velocity (PWV) has been recognized as a noninvasive method of accessing

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Table 1. Clinical Variables of the Kidney Transplantation Patients and Control Group

Items	All (n = 120)	KT (n = 55)	Control (n = 65)	*P* Value
Age (y)	52.56 ± 7.37	51.40 ± 9.39	53.54 ± 4.93	.113
Height (cm)	162.67 ± 8.37	162.09 ± 8.58	163.15 ± 8.22	.490
Body weight (kg)	63.69 ± 11.07	62.07 ± 12.93	65.06 ± 9.10	.141
Waist circumference (cm)	84.41± 10.02	84.76 ± 12.08	84.11 ± 7.96	.722
Body mass index (BMI; kg/m^2)	24.03 ± 3.64	23.57 ± 4.40	24.42 ± 2.70	.204
White blood count (×1000/uL)	6.74 ± 2.02	7.11 ± 2.35	6.42 ± 1.64	.062
Hemoglobin (g/dL)	13.63 ± 2.19	12.41 ± 2.33	14.67 ± 1.40	<.001*
Total cholesterol (mg/dL)	181.47 ± 44.73	192.53 ± 46.16	172.11 ± 41.58	.012*
Triglyceride (mg/dL)	162.03 ± 135.96	152.58 ± 117.51	170.03 ± 150.25	.368
HDL-C (mg/dL)	50.44 ± 13.56	51.07 ± 14.99	49.91 ± 12.31	.641
LDL-C (mg/dL)	107.65 ± 36.31	114.52 ± 41.61	101.85 ± 30.28	.056
Fasting glucose (mg/dL)	112.93 ± 37.85	110.98 ± 47.80	114.57 ± 27.02	.607
Blood urea nitrogen (mg/dL)	20.43 ± 10.93	25.65 ± 13.71	16.00 ± 4.50	<.001*
Creatinine (mg/dL)	1.39 ± 0.82	1.79 ± 1.05	1.05 ± 0.26	<.001*
Systolic blood pressure (mmHg)	135.10 ± 16.55	137.84 ± 15.78	132.78 ± 16.95	.096
Diastolic blood pressure (mmHg)	81.47 ± 11.79	86.95 ± 10.56	76.83 ± 10.79	<.001*
Intact parathyroid hormone (pg/mL)	88.20 ± 85.33	134.90 ± 106.12	48.69 ± 24.03	<.001*
cfPWV (m/s)	8.96 ± 3.11	9.13 ± 3.35	8.82 ± 2.91	.595
Leptin (ng/mL)	30.75 ± 31.73	48.85 ± 34.56	19.67 ± 24.32	<.001*
Arterial stiffness				
No	83 (69.2%)	38 (69.1%)	45 (69.2%)	.987
Yes	37 (30.8%)	17 (30.9%)	20 (30.8%)	
Gender				
Male	64 (53.3%)	27 (49.1%)	37 (56.9%)	.392
Female	56 (46.7%)	28 (50.9%)	28 (43.1%)	
Diabetes				
No	57 (47.5%)	22 (40.0%)	35 (53.8%)	.130
Yes	63 (52.5%)	33 (60.0%)	30 (46.2%)	
Hypertension				
No	83 (69.2%)	42 (76.4%)	41 (63.1%)	.116
Yes	37 (30.8%)	13 (23.6%)	24 (36.9%)	

Data are expressed as means ± SDs and were analyzed by the Student *t* test or Mann-Whitney *U* statistic (BUN, Cr, TG, fasting glucose, iPTH, leptin).
Data are expressed as number of patients and analysis by χ^2 test.
Abbreviations: HDL-cholesterol, high-density lipoprotein cholesterol; LDL-cholesterol, low-density lipoprotein cholesterol; GFR, glomerular filtration rate; cfPWV, carotid-femoral pulse wave velocity.
*$P < .05$ was considered statistically significant.

vascular function and is the gold standard indicator of arterial function and structure, as noted in the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC) guidelines [6].

Studies had shown that there is crosstalk between cardiovascular diseases and adipokines, such as adiponectin, resistin, and leptin [7,8]. Among these adipokines, leptin is a 16-kDa peptide hormone mainly produced by white adipose tissue that acts as a major secretory and endocrine organ involved in a wide range of functions beyond fat storage. Classic effects of leptin include food intake reduction and increasing energy expenditure, and its levels are directly associated with white adipose tissue [9]. High leptin levels are implicated in metabolic, inflammatory, and homeostatic factors involved in obesity, HTN, and other cardiovascular diseases [10–12]. In addition, previous studies reported elevated leptin levels linked to chronic kidney disease (CKD) [13,14] and hyperleptinemia is observed in patients with end-stage renal disease who underwent hemodialysis or peritoneal dialysis, which indicated altered leptin production as well as excretion by terminal renal failure [15–17]. Furthermore, leptin stimulated the renin-angiotensin-aldosterone system, leading to increase of blood pressure, and inducing vascular smooth muscle cell proliferation, endothelial oxidative stress, and reactive oxygen species formation, and resulting in aortic mechanical dysfunction that then contributed to arterial stiffness [11,18,19]. In this study, we aimed to observe the serum concentration of leptin in KT patients compared with the normal population and examine the influences of leptin on arterial stiffness in KT patients.

MATERIALS AND METHODS

Patients

The study was an observational cross-sectional study and conducted at a medical center from May through August 2013 in Hualien, Taiwan, where 55 KT patients were enrolled. There were 65 age-matched controls subjects enrolled from the health examination outpatient department as the control group at the same hospital at the same time. All participants provided their written informed consent to participate in this study. The Protection of the Human Subjects Institutional Review Board of Tzu-Chi University and Hospital approved the study