Subclinical Peripheral Arterial Disease in Renal Transplantation

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Abstract: *Background:* Peripheral arterial disease (PAD) is a common finding in patients at various stages of chronic kidney disease; however, there has only been a limited amount of data that have been published regarding the prevalence and associated risk factors of subclinical PAD in renal transplant recipients. *Methods:* The authors cross sectionally investigated the prevalence of PAD using ankle-brachial index (ABI) in 304 renal transplant recipients with no previous diagnosis of PAD. Patients were considered to have subclinical PAD when ABI <0.9. The authors also determined the associated risk factors for subclinical PAD. *Results:* The mean age of the 304 patients was 53 years, and 30 patients (9.9%) had a history of atherosclerotic event (including past cardiovascular and cerebrovascular events). Twenty-five of the 304 patients (8%) had ABI <0.9 and 1 had (0.3%) ABI >1.3. Compared to patients with normal ABI, a history of atherosclerotic events is the only independent risk factor for patients with subclinical PAD ($P = 0.0468$). *Conclusions:* Subclinical PAD is an inadvertent issue in renal transplant patients, especially those with a history of atherosclerotic events. Further research is needed on the long-term clinical impact and optimal treatment of subclinical PAD among renal transplant patients.

Key Indexing Terms: Atherosclerotic events; Ankle-brachial index; Brachial-ankle pulse wave velocity; Peripheral arterial disease; Renal transplantation. **[Am J Med Sci 2014;347(4):267–270.]**

Peripheral arterial disease (PAD) is a common comorbidity and is associated with considerable morbidity and mortality among patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD).[1–5] Even after successful renal transplantation, PAD still seems a risk factor of cardiovascular morbidity.[6] However, data is limited regarding its prevalence and the associated risk factors in renal transplant recipients, especially those without obvious clinical manifestations of PAD. Ankle-brachial index (ABI) is a noninvasive diagnostic test that is easy to perform, reproducible and efficient in detecting PAD. An ABI <0.9 is very highly sensitive and specific for angiographically documented PAD for arterial stenosis greater than 50% in the lower extremities.[7] Therefore, it is a useful tool to help clinicians to diagnose subclinical PAD in clinical practice. Furthermore, brachial-ankle pulse wave velocity (BaPWV) is relatively easy to obtain and is a potential marker of arterial stiffness and even cardiovascular risk; however, the association between the level of BaPWV and subclinical PAD has also been undetermined.[8]

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In this cross-sectional study, we investigated the prevalence and the associated risk factors of subclinical PAD using ABI in renal transplant recipients with no previous diagnosis of PAD. We also determined the association between the level of BaPWV and subclinical PAD.

MATERIALS AND METHODS

Subjects

This cross-sectional study involved 304 patients, who had received renal transplantation for at least 3 months and regular follow-up at Chung Shan Medical University (Taichung, Taiwan). All of the patients were in a stable clinical condition and free from recent acute rejection, infection or cardiovascular events (within 3 months) prior to this enrollment. We excluded patients with a history of PAD (defined as an atherosclerotic disease that causes ischemia in the legs, confirmed by arteriography or vascular Doppler, or those treated with surgery, stent or amputations). The local institutional review board approved this study (CS07146), and written informed consent was obtained from each participant.

ABI and BaPWV Measurements

All measurements were performed in a quiet environment by one single well-trained investigator. We used an automatic device (model VP 1000; Nippon Cohn, Komaki, Japan) to measure ABI and BaPWV for each participant after at least 5 minutes of supine rest.[9] To calculate ABI, we divided the systolic blood pressure (SBP) in each lower leg by the SBP in the arm. The higher brachial SBP is usually chosen for calculation, but only brachial SBP of a nonfistula arm was chosen in patients with established fistula. The lowest ABI value less than 0.9 was regarded as PAD. The value of BaPWV was determined from the side of body with lower ABI, and subsequent statistical analyses were performed with these values.

Laboratory Measurements

Fasting blood samples were obtained for assay. Serum hematocrit, calcium, phosphorus, total cholesterol, low-density lipoprotein cholesterol, triglycerides and intact parathyroid hormone were determined using standard methodology in the qualified laboratory at Chung Shan Medical University Hospital. For serum creatinine, a time-averaged mean of the last 3 months was calculated and the glomerular filtration rate (GFR) was estimated using the Cockcroft-Gault equation. Serum high-sensitivity C-reactive protein was measured using a high-sensitivity monoclonal antibody to C-reactive protein coated on polystyrene beads (Siemens Healthcare Diagnostics, Germany). High-sensitivity C-reactive protein was measured twice, 1 month apart to calculate the averaged values.

Covariates

The following information was collected for all subjects: demographics, comorbidities (including hypertension, diabetes mellitus (DM), dyslipidemia, hepatitis B, hepatitis C and

a history of atherosclerotic event), dialysis vintage, immunosuppressive regimen and smoking status. A history of atherosclerotic events was defined as a typical history of angina with abnormal coronarography or myocardial scintigraphy, myocardial infarction, transient cerebral ischemia, stroke or any revascularization procedure.

Statistical Analyses

All analyses were performed using SPSS software for Windows (Version 14.0; SPSS, Chicago, IL). The unpaired *t* test or the Wilcoxon's rank sum test was used to compare group means of normally and not normally distributed variables, respectively. The χ^2 test was used for qualitative variables. The stepwise multiple logistic analysis was used to evaluate which factors were independently associated with subclinical PAD. Predictors were selected based upon significant findings in the present analysis. A *P* value of less than 0.05 was considered as statistically significant.

RESULTS

The demographic and hemodynamic parameters of 304 patients are shown in Table 1. Two hundred seventy-eight patients (91%) had a normal ABI, 25 (8%) had an ABI <0.9 and 1 (0.3%) had an ABI >1.3. None of the 25 patients with ABI <0.9 reported symptoms of numbness, coldness, typical intermittent claudication or resting pain. The differences of

TABLE 1. Comparison of baseline characteristics in patients with and without subclinical PAD

	Total (N = 303)	ABI < 0.9 (n = 25)	0.9 < ABI < 1.3 (n = 278)	*P*
ABI	1.0 ± 0.1	0.8 ± 0.1	1.1 ± 0.1	<0.0001*
Age (yrs)	53 ± 10.7	58.0 ± 12.0	52.5 ± 10.5	0.0137*
Male gender (%)	166 (54.8)	12 (48.0)	153 (55.0)	0.4986
BMI	24.2 ± 3.9	26.5 ± 5.1	24.0 ± 3.7	0.0253*
Past smoker (%)	50 (16)	12 (48.0)	70 (25.2)	0.0139*
Current smoker (%)	82 (27)	8 (32.0)	42 (15.1)	0.0293*
Modality of dialysis (%)				0.8260
PD	43 (14.1)	3 (12.0)	39 (14.0)	
HD	240 (79.0)	20 (80.0)	220 (79.1)	
Preemptive transplantation	21 (6.9)	2 (8.0)	19 (6.9)	
Duration of dialysis, median, (range), mo	18 (0–204)	22.8 ± 24.4	27.9 ± 33.2	0.4587
Immunosuppressive regimen (%)				
CsA based	46 (15.1)	5 (20.0)	41 (14.8)	0.7154
FK506 based	253 (83.2)	20 (80.0)	232 (83.5)	
Sirolimus based	5 (1.7)	0 (0.0)	5 (1.7)	
Preexisting DM (%)	39 (12.8)	10 (40.0)	28 (10.1)	<0.0001*
NODM (%)	55 (18.1)	4 (16.0)	51 (18.4)	0.7707
HTN (%)	209 (68.8)	20 (80.0)	188 (67.6)	0.2015
Dyslipidemia (%)	164 (54.0)	15 (60.0)	148 (53.2)	0.5159
Hepatitis B (%)	39 (12.8)	4 (16.0)	35 (12.6)	0.6258
Hepatitis C (%)	37 (12.2)	5 (20.0)	32 (11.5)	0.2143
History of atherosclerotic events (%)	30 (9.9)	8 (32.0)	22 (7.1)	0.0014*
Time since transplantation, median (range), mo	58.5 (12–215)	15 (0–102)	18 (0–204)	0.7341
Systolic BP (mm Hg)	131.5 ± 18.0	138.7 ± 20.2	130.9 ± 17.7	0.0362*
Diastolic BP (mm Hg)	78.9 ± 10.7	78.0 ± 12.6	79.0 ± 10.6	0.6702
Pulse pressure (mm Hg)	52.6 ± 13.4	60.7 ± 12.3	51.9 ± 13.3	0.0020*
Hematocrit (%)	40.0 ± 5.2	39.9 ± 5.3	40.0 ± 5.1	0.9515
hs-CRP (mg/dL)	0.2 ± 0.4	0.2 ± 0.2	0.2 ± 0.4	0.1350
Ca (mg/dL)	10.1 ± 0.8	10.1 ± 0.6	10.1 ± 0.8	0.8900
P (mg/dL)	3.0 ± 0.6	3.1 ± 0.5	3.0 ± 0.6	0.2326
Intact PTH (pg/dL)	95.5 ± 81.6	106.2 ± 103.1	94.6 ± 79.5	0.4943
Triglycerides (mg/dL)	132.2 ± 96.6	174.4 ± 210.1	128.4 ± 78.6	0.2869
Total cholesterol (mg/dL)	184.7 ± 40.8	192.6 ± 38.8	184.0 ± 40.9	0.3111
LDL (mg/dL)	101.9 ± 30.7	102.8 ± 27.9	101.8 ± 31.0	0.8780
Creatinine (mg/dL)	1.3 ± 0.5	1.3 ± 0.4	1.3 ± 0.5	0.8262
eGFR (mL/min)	55.8 ± 17.2	59.0 ± 18.1	58.3 ± 17.9	0.8624
BaPWV (cm/s)	1497.6 ± 328.9	1516.2 ± 538.5	1495.9 ± 304.6	0.8538

Data are shown as numbers with percentage or means ± standard deviation or median (range).

* Statistically significant.

ABI, ankle-brachial index; BaPWV, brachial-ankle pulse wave velocity; BMI, body mass index; BP, blood pressure; CsA, cyclosporine; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HD, hemodialysis; hs-CRP, high-sensitivity C-reactive protein; HTN, hypertension; Intact PTH, intact parathyroid hormone; LDL, low-density lipoprotein; NODM, new-onset diabetes mellitus; PD, peritoneal dialysis.