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Original article

Association between estimated glomerular filtration rate and peripheral arterial disease

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ABSTRACT

Background: Chronic kidney disease (CKD) is an evolving paradigm for the risk assessment of cardiovascular diseases. We hypothesized that an advanced stage of CKD may predict the presence of peripheral arterial disease (PAD).

Methods: Screening for PAD by an ankle-brachial pressure index (ABI) ≤0.9 was conducted in a consecutive series of 583 subjects (mean age 68.1 ± 12.9 years, 411 men). Levels of estimated glomerular filtration rate (eGFR) and factors associated with the presence of PAD were examined.

Results: Sixty patients (10.3%) had PAD and 192 patients (32.9%) had eGFR <60 mL/min/1.73 m^2 among all subjects. In patients with an advanced stage of CKD (stage ≥3, equivalent to eGFR <60 mL/min/1.73 m^2), high prevalence of PAD (17.2%) and lower ABI levels (1.04 ± 0.18) were observed. Univariate analyses revealed that PAD was associated with an advanced stage of CKD [odds ratio (OR) 1.850, 95% confidence interval (CI) 1.322–2.588, $p < 0.001$], as well as age, male gender, systolic blood pressure, and hemoglobin A1c. Multivariate logistic regression analyses revealed that PAD was independently predicted by the CKD stages (OR 1.498, 95% CI 1.011–2.220, $p = 0.044$, adjusted for covariates).

Conclusions: An advanced stage of CKD is independently and significantly associated with the presence of PAD. Targeted screening with ABI measurement can be beneficial in patients with CKD.

Introduction

Atherosclerosis is still a leading cause of death in industrialized countries. The Framingham Heart Study [1] and the NIPPON DATA80 [2] research have demonstrated that the progression of systemic atherosclerosis leads to an accumulation of cardiovascular risk factors and may result in the development of polyvascular disease. Based on these large-scale cohort studies, the Framingham Risk Sore [1] and the NIPPON DATA80 chart [2] for the Japanese population have been developed to predict an individual's risk of a future coronary artery event or stroke.

Lower-extremity peripheral arterial disease (PAD) can be a manifestation of systemic atherosclerosis [3,4] and the morbidity has been associated with an elevated risk of cardiovascular disease. Although PAD screening for high-risk patients and early treatment intervention are essential, there is still no system which has been established for predicting the presence of PAD by calculating traditional risk factors or biomarkers. In fact, 12.3% of patients who have low cardiovascular risk with Framingham scores have shown an abnormal ankle brachial index (ABI) [5], which represents the presence of PAD [3,6,7].

Recent studies have demonstrated that individuals with chronic kidney disease (CKD) are more likely to develop atherosclerotic cardiovascular diseases [8–11]. Importantly, the comorbidity of PAD and CKD is strongly indicative of an individual at high risk [12]. Although ethnic-specific variations in the prevalence of PAD have been reported [13,14], large-scale clinical studies from Asian population are limited. The morbidity of PAD in the general Japanese population aged 40 years or over is 1.47% [15] and that in diabetic patients is 7.6% [16]. Markedly high PAD prevalence of 23.8% [17] and even 47.2% [18] have been reported in Japanese patients undergoing hemodialysis; however, the association between PAD and CKD has not been fully investigated. The aim of this study was to evaluate the prevalence of PAD and its

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association with CKD in Japanese patients, and to examine whether low levels of estimated glomerular filtration rate (eGFR) can predict the presence of PAD.

Materials and methods

Study patients

Data were collected from a consecutive series of 583 patients examined with ABI on admission. These patients were hospitalized for examination and/or treatment of the following cardiovascular diseases: 54.8% were ischemic heart disease, 18.5% were heart failure due to valvular and/or myocardial disease, and 20.4% were for arrhythmia or others. We excluded patients with a cardiovascular emergency, unstable coronary artery disease, or decompensated heart failure, and also patients on hemodialysis. The study was performed in accordance with the Declaration of Helsinki and with Good Clinical Practice. Patients were managed according to the recommended guidelines of the Japanese Circulation Society. Data were analyzed anonymously, because this study was performed retrospectively without informed consent.

ABI measurement

The systolic blood pressure (BP) in the right and left brachial arteries, dorsalis pedis arteries, and posterior tibial arteries was measured using Form (Omron Colin, Tokyo, Japan) after the patient had rested in the supine position for at least 10 min. For each leg, the higher of the BP values in the dorsalis pedis and posterior tibial arteries was divided by the higher of the left and right arm brachial BP values, and the lower of the two results (right and left leg) was used as ABI in all analyses [19]. The presence of PAD was defined by an ABI $\leq$0.9 [3,20].

Renal function

Levels of eGFR of all patients were calculated from the serum creatinine levels, using the following equation established by the Japanese Society of Nephrology: eGFR (mL/min/1.73 m^2) = 194 $\times$ serum creatinine level$^{-1.094}$ $\times$ age$^{-0.287}$ ($\times$0.739 if female) [21]. The stages of CKD were classified based on the levels of eGFR: stage 1 (eGFR $\geq$90 mL/min/1.73 m^2), stage 2 (eGFR 60–89 mL/min/1.73 m^2), stage 3 (eGFR 30–59 mL/min/1.73 m^2), stage 4 (eGFR 15–29 mL/min/1.73 m^2), and stage 5 (eGFR $<$ 15 mL/min/1.73 m^2).

Coronary risk factors

We examined low-density lipoprotein cholesterol (LDL-C) and hemoglobin A1c (HbA1c). Clinical characteristics of the study population were derived from interviews or history of or treatment for the morbidities with the following criteria: hypertension was blood pressure $\geq$140/90 mmHg, dyslipidemia was LDL-C $\geq$140 mg/dL, and/or triglycerides $\geq$150 mg/dL, diabetes mellitus was HbA1c $\geq$6.1% of the National Glycohemoglobin Standardization Program, and hyperuricemia was uric acid $\geq$7.0 mg/dL in accordance with screening criteria of each clinical guideline.

Statistical analysis

Categorical variables were expressed as absolute frequency and relative frequency (percentage) and compared using the χ^2 test. Continuous variables were expressed as mean $\pm$ standard deviation and were compared using the Mann–Whitney test. One-way analysis of variance (ANOVA) with the Kruskal–Wallis test and Dunnett's multiple comparisons test was used to compare ABI levels between CKD stages. The magnitude of the association between patient characteristics and the presence of PAD was quantified in terms of the odds ratio (OR) and the 95% confidence interval (CI) using univariate logistic regression analyses. Multiple logistic regression analyses were then performed with adjustments for significant parameters, apart from multicollinear variables, to determine the subset of independent variables for predicting PAD. We assessed the diagnostic accuracy of variables by using a receiver operating characteristic (ROC) curve [22]. A p-value $<$0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics 18 (IBM Co., Armonk, NY, USA).

Results

Table 1 summarizes the clinical characteristics of the study population and the categories of renal function. The study population consisted of 583 hospitalized patients (mean 68.1 $\pm$ 12.9 years, 411 men). Sixty patients (10.3%) had PAD and 192 patients (32.9%) showed renal insufficiency, defined as a eGFR level $<$60 mL/min/1.73 m^2. The prevalence of hypertension, dyslipidemia, diabetes, smoking, and hyperuricemia in the study population

Table 1
Clinical characteristics of the study population and categories of renal function.

Characteristics	All (n = 583)	eGFR $<$60 mL/min/1.73 m^2 (n = 192)	eGFR $\geq$60 mL/min/1.73 m^2 (n = 391)	p-Value
Age, years	68.1 $\pm$ 12.9	73.7 $\pm$ 8.9	65.4 $\pm$ 13.6	$<$0.001
Male, n (%)	411 (70.5)	152 (79.2)	259 (66.2)	0.001
ABI	1.08 $\pm$ 0.17	1.04 $\pm$ 0.18	1.11 $\pm$ 0.15	$<$0.001
ABI $\leq$0.9, n (%)	60 (10.3)	33 (17.2)	27 (7.0)	$<$0.001
eGFR, mL/min/1.73 m^2	68.86 $\pm$ 23.52	46.26 $\pm$ 11.68	80.04 $\pm$ 19.40	$<$0.001
Hypertension, n (%)	387 (66.4)	146 (76.0)	241 (61.6)	0.001
Dyslipidemia, n (%)	269 (45.1)	100 (52.1)	169 (43.2)	0.049
Diabetes, n (%)	169 (29.0)	71 (37.0)	98 (25.1)	0.003
Smoking, n (%)	286 (49.1)	104 (54.2)	182 (46.5)	0.090
Hyperuricemia, n (%)	78 (13.4)	44 (22.9)	34 (8.7)	$<$0.001
Family history, n (%)	117 (20.1)	46 (24.0)	71 (18.2)	0.124
Ischemic heart disease, n (%)	320 (54.8)	117 (60.9)	203 (51.9)	0.046
Vascular disease, n (%)	102 (17.5)	37 (19.3)	65 (16.6)	0.445
Arrhythmia, n (%)	119 (20.4)	36 (18.3)	83 (21.2)	0.467
Valvular disease, n (%)	45 (7.7)	14 (7.3)	31 (7.9)	0.774
Cardiomyopathy, n (%)	34 (5.8)	8 (4.2)	26 (6.6)	0.224
Heart failure, n (%)	29 (5.0)	12 (6.3)	17 (4.3)	0.328

eGFR, estimated glomerular filtration ratio; ABI, ankle-brachial index.