Is Chronic Kidney Disease Associated with a High Ankle Brachial Index in Adults at High Cardiovascular Risk?

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Aim: Chronic kidney disease (CKD) is an important risk factor for cardiovascular disease (CVD) events. A high ankle brachial index (ABI), a marker of lower arterial stiffness, is associated with CVD events. It remains unknown whether high ABI is associated with CKD. The objectives of this study were to determine the association of CKD with high ABI in adults at high CVD risk.

Methods: The study enrolled hospital-based patients at high CVD risk and measured kidney function and ABI. The glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease (MDRD) equation and ABI was categorized as low (<0.90), low-normal (0.90 to 1.09), normal (1.10 to 1.40), and high (≥1.40 or incompressible). Logistic regression was used to evaluate the associations of CKD with ABI categories.

Results: Among 6412 participants, 25% had CKD, 25% had an ABI measurement <0.90, and 1% had an ABI >1.40. In models adjusted for age, sex, hypertension, diabetes, body mass index, low-density and high-density lipoprotein cholesterol, and smoking, only low ABI was associated with an increased risk of CKD; however, both low ABI (OR: 2.1, 1.6-2.8) and high ABI (OR: 2.4, 1.0-6.4) were associated with an increased risk of CKD in diabetic individuals. Additionally, only low ABI was associated with advanced eGFR levels.

Conclusions: High ABI values are associated with an increased risk of CKD in diabetic individuals at high cardiovascular risk. Future studies are required to speculate whether high ABI might lead to diminished kidney function through nonatherosclerotic pathways and to understand the mechanisms linking them to CVD events and diabetes.


Key words: Chronic kidney disease, Ankle brachial index, Cardiovascular risk, Diabetes

Introduction

Chronic kidney disease (CKD) is strongly associated with cardiovascular disease (CVD) events and all-cause mortality. These associations cannot be fully explained by traditional CVD risk factors, and are identified even with modest decrements in kidney function. The mechanisms involved in the connection between CKD and CVD are probably numerous. Vascular calcification, such as coronary artery calcification, is considered to be the causal link between them. Vascular calcification is highly prevalent, developing early and contributing to the markedly increased cardiovascular risk, in CKD patients. However, increased knowledge about the mechanisms of calcification together with improved imaging techniques have provided evidence that vascular calcification should be divided into two distinct entities according to the specific site of calcification within the vascular wall: plaque calcification, involving patchy...
calcification of the intima in the vicinity of lipid or cholesterol deposits, and calcification of the media in the absence of such lipid or cholesterol deposits, known as Mönckeberg-type atherosclerosis.\(^7\,9\)

The ankle brachial index (ABI) is widely accepted as an established clinical test for the assessment of peripheral arterial disease (PAD) and an indicator of generalized atherosclerosis.\(^10\) Furthermore, the greatest relevance of the ABI may not be for the limb but rather as a biomarker of cardiovascular risk.\(^11\,12\) A low ABI has been reported to associate with increased mortality and the risk of prevalent cardiovascular disease.\(^13\) Alternatively, a high ABI reflects generalized stiffening of the lower limb arteries,\(^14\,15\) and an elevated ankle systolic blood pressure has high specificity for medial arterial calcification (MAC).\(^16\)

Although previous studies have reported that CKD is associated with a low ABI\(^17\,19\), the association of CKD with a high ABI has not been well studied. A recent study conducted by Ix and colleagues showed that CKD is associated with the high extremes of ABI in older people,\(^20\) which suggests that MAC may begin early in the process of kidney dysfunction; however, such an association was only identified in a community-based population. Thus, we evaluated the association of CKD with a high ABI and compared the strength of association to that with a low ABI in a hospital-based cohort of patients at high cardiovascular risk.

### Methods

#### Participants

The study is a hospital-based study of Chinese patients that was designed to evaluate the risk factors for PAD and the relationship between ABI and mortality from all-cause and CVD in Chinese patients at high cardiovascular risk (over 50 years old with 2 or more cardiovascular risk factors). The study design has been described previously.\(^21\,22\) In brief, 6449 subjects were recruited from 8 university hospitals in Beijing and Shanghai. The present study represents cross-sectional analysis using data from the July to November 2004 medical records, in which ABI and kidney function were measured concurrently. Prescription medications (ACEI/ARB, antiplatelet drugs and statins) in all patients are shown in Table 1. Among the 6449 subjects, 37 (0.5%) were excluded because of missing ABI or kidney function measurement, resulting in a study sample of 6412 subjects for this analysis. All participants provided written informed consent, and the study was approved by the ethics committee of the involved 8 universities.

#### Blood Samples

Blood samples were drawn in a fasting state. Serum creatinine, urea nitrogen, and uric acid were measured by standard laboratory techniques using an autoanalyzer. Blood glucose was measured enzymatically with a glucose oxidase method. Triglycerides, HDL-cholesterol and total cholesterol were assessed with commercial enzymatic kits (Roche Diagnostics, Basel, Switzerland). LDL-cholesterol was calculated according to the Friedewald formula.

#### ABI Measurement

Doppler ultrasound (Nicolet Vascular, Elite 100R, USA) was used to measure systolic blood pressure (SBP) in the bilateral brachial, tibial and dorsal pedal arteries while supine after a 5-min rest. The occluding cuffs (55 × 12.5 cm) were applied just above the malleoli to measure ankle pressure. The Doppler probe was used at a frequency of 5MHz. Right and left ABI were calculated from the highest pressure in the dorsal or posterior tibial arteries on the right and left sides, respectively, and by the highest brachial pressure on either side.

#### Renal Function

The estimated glomerular filtration rate (eGFR) was calculated using a new equation developed by tailoring the Modification of Modification of Diet in Renal Disease equation (MDRD) to data from Chinese patients with CKD.\(^23\) eGFR (mL/min per 1.73 m\(^2\)) = 175 × (serum creatinine\(^{-1.234}\)) × (age\(^{-0.179}\)) × 0.79 (if female). Chronic kidney disease was defined as eGFR < 60 mL/min per 1.73 m\(^2\).\(^24\)

#### Statistical Analysis

The natural cubic spline functions were adopted to evaluate parametric nonlinear functions for eGFR and ABI measurements. Because prior studies consistently showed a higher risk for all-cause mortality and CVD events among people with an ABI < 0.9 or > 1.4,\(^25\,27\) we developed mutually exclusive categories that simultaneously captured the functional form of the spline analysis and also utilized these cut-off points (< 0.90, 0.90 to 1.09, 1.10 to 1.40, and > 1.40/incompressible). Subjects with ABI measurements of 1.10 to 1.40 served as the reference group for subsequent analyses. Multinomial logistic regression was conducted to evaluate the associations of CKD with a low and high ABI simultaneously. SPSS statistical software (version 16) (SPSS, Inc., Chicago, Illinois) was used for analyses.
Results

Among the 6412 study participants, the mean age was 67 years and 46.4% were female. Chronic kidney disease was detected in 24.8% \((n=1582)\). Twenty-five percent of participants \((n=1576)\) had an ABI \(<0.90\), 42% \((n=2717)\) between 0.90 and 1.09, 32% \((n=2048)\) between 1.10 and 1.40, and 1% \((n=71)\) \(>1.40\).

Compared with a participant with an ABI between 1.10 and 1.40, lower ABI participants were older, less frequently male, had a higher prevalence of hypertension, diabetes, stroke, myocardial infarction and unstable angina pectoris, and were more likely to have higher UA and BUN levels. In contrast, participants with high ABI did not differ significantly by age. With the exception of male sex, uric acid, and blood urea nitrogen, high ABI was not associated with traditional CVD risk factors (Table 1).

We evaluated the association of kidney function as a continuous variable with ABI measurements (Fig. 1). Overall, the spline function showed a bell-shaped relationship, wherein individuals with either a high or low ABI had a lower eGFR than individuals...
with intermediate ABI measurements (Panel A); however, the bell-shaped curve was more obvious in diabetic than non-diabetic individuals (Panel B vs Panel C). Both diabetic and non-diabetic individuals with most preserved kidney function (highest eGFR) were centered at an ABI measurement of 1.20.

When defined by eGFR, CKD was associated with an approximately 2.4-fold risk of an ABI <0.9 compared with subjects with ABI measurements of 1.10 to 1.40 in unadjusted analyses. The association of CKD with ABI <0.90 was moderately attenuated in the fully adjusted model, but CKD remained significantly associated with a 1.7-fold risk of a low ABI. In contrast, no significant association of CKD with an ABI >1.40 was observed. Next, we evaluated the association of each kidney function measure with the ABI category, stratified by the diabetes status. The association of CKD with a low ABI seemed similar in people with or without diabetes. The association of CKD with a high ABI, however, was qualitatively stronger among subjects with diabetes (OR=2.4, 95%CI: 1.0-6.4) (Table 2). Also, we evaluated the converse association. In addition to the risk of low ABI, the association of high ABI with eGFR levels was not identified in the present series (Table 3).

**Discussion**

The Strong Heart Study is the only study to date that has prospectively evaluated the clinical significance of a high ABI (>1.40) in detail. Individuals in the Strong Heart Study with high ABI values had higher levels of several CVD risk factors than those with normal ABI values (0.9-1.40); however, the results from the Atherosclerosis Risk in Communities (ARIC) Study indicated that, in low risk populations, individuals with a high ABI were not characterized by a more adverse atherosclerosis risk factor profile and did not suffer greater CVD event rates than those with a normal ABI. Although a high ABI may identify individuals at higher risk for CVD events, it is uncertain whether this association is entirely independent of atherosclerosis.

A recent study showed that CKD was associated with an extremely high ABI in community-living older people, which may provide novel insights into the mechanisms of CVD in subjects with kidney disease; however, the primary finding of our study did not completely support their hypothesis. In our series, we did not observe a significant association of CKD with a high ABI in adjusted models, but after stratification by diabetes status, the association of CKD with a high ABI was qualitatively stronger among subjects

![Fig. 1. Estimated GFR by Ankle brachial index. Natural cubic spline function: A) in all individuals; B) in diabetic individuals; C) in non-diabetic individuals.](image-url)
with diabetes, in agreement with the finding of Ix et al.\textsuperscript{20}. MAC is thought to lead to high ABI measurements in the majority of cases\textsuperscript{14, 15}. Furthermore, the study showed that a high ABI value directly correlated with MAC severity, as determined by lower limb plain X-ray\textsuperscript{16}. MAC is characterized by a diffuse distribution that may directly contribute to arterial stiffness\textsuperscript{29, 30}. Among maintenance dialysis patients, MAC has been associated with increased left ventricular mass and aortic pulse-wave velocity\textsuperscript{29}, which may lead to cardiac fibrosis and increased arrhythmia risk. If similar relations extend to people without severe kidney disease, a high ABI might indicate an elevated risk for CVD events and mortality by mechanisms entirely distinct from atherosclerosis. In addition, findings from the ARIC study showed a lower prevalence of hypertension in those with a high ABI\textsuperscript{28}. These results indicate that the factors that lead to a modestly high ABI are likely due to a complex vascular pathophysiology.

Diabetes has also been shown to be a risk factor for either a high or low ABI\textsuperscript{31}. The effects of diabetes are complex, as this condition is associated with both atherosclerosis and MAC of the peripheral arteries. In the present series, compared to individuals with normal ABI, the prevalence of diabetes was not higher in individuals with a high ABI; however, a suggestive association was found between an ABI $'1.40 and CKD in the present series, stratified by diabetes status, with approximately equal strength to the association of CKD with a low ABI. Furthermore, ACEI plus ARB may lead to worse renal outcomes in a broad population. Additionally, the landmark JUPITER trial reported that CKD patients achieved a 44% reduction in mortality when they were treated with statins compared to patients treated with a placebo\textsuperscript{32}. In the present study, more than 50% of the patients were treated with ACEI/ARB and more than 30% of the patients were treated with statin. Thus, we should be cautious about drawing conclusions before evaluating the influence of medications.

The strengths of this study include its hospital-based setting, Chinese ethnic group, large sample size and uniform measurement of creatinine, ABI and multiple potential confounding variables. This study also has important limitations. First, the cross-sectional study design does not allow evaluation of temporality. In addition, the standard method of reporting ABI has always been to compare the highest systolic pressures from the ankle and arm; however, using the highest artery pressure in the leg to calculate the
index may cause a group of patients at high cardiovascular risk to be overlooked. Several methods have been described to eliminate this underestimation. One method is to take the higher pressure for the dorsalis pedis and posterior tibial in each leg, calculate the ABI using each measure, and then use the lower of the two indexes, which was adopted in the present study. Finally, because the prevalence of a high ABI was only 1% ($n=71$) in our study sample, we had imprecise estimates of the strength of association, as shown by the relatively wide confidence intervals; however, a bell-shaped relationship, wherein individuals with either a high or low ABI had a lower eGFR, might give an insight into the mechanism of medial arterial calcification.

**Conclusions**

High ABI measurements are associated with an increased risk of CKD in diabetic individuals at high cardiovascular risk, but not vice versa. Although much is known about the risk factors and consequences of atherosclerotic PAD, future studies are required to elucidate whether high ABI might lead to diminished kidney function through nonatherosclerotic pathways and to understand the mechanisms linking them to CVD events and diabetes.

**Conflict of Interests**

none.

**References**

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