High Prevalence of Peripheral Arterial Disease in Persons With Renal Insufficiency

Results From the National Health and Nutrition Examination Survey 1999–2000

Ann M. O’Hare, MD, MA; David V. Glidden, PhD; Caroline S. Fox, MD, MPH; Chi-yuan Hsu, MD, MSc

Background—Although renal insufficiency is a recognized risk factor for coronary artery disease, little is known about the epidemiology of lower-extremity peripheral arterial disease (PAD) in persons with renal insufficiency.

Methods and Results—We examined the cross-sectional association of PAD, defined as an ankle-brachial index (ABI) <0.9, and renal insufficiency, defined as an estimated creatinine clearance (CRCL) <60 mL · min⁻¹ · 1.73 m⁻², among 2229 eligible participants in the National Health and Nutrition Examination Survey (NHANES) 1999 to 2000. An estimated 1.2 ± 0.3 million persons ≥40 years old with CRCL <60 mL · min⁻¹ · 1.73 m⁻² (24%) have PAD defined as an ABI <0.9 (versus 3.7% of persons with CRCL ≥60 mL · min⁻¹ · 1.73 m⁻²). The association of ABI <0.9 with renal insufficiency was independent of potential confounders such as age, diabetes, hypertension, coronary artery disease, stroke history, and hypercholesterolemia (OR 2.5, 95% CI 1.2 to 5.1, P = 0.011, referent category ABI 1.0 to 1.3).

Conclusions—Clinicians should be aware of the remarkably high prevalence of PAD among patients with renal insufficiency. In the clinical setting, accurate identification of patients with renal insufficiency combined with routine ABI measurement in this group would greatly enhance efforts to detect subclinical PAD. (Circulation. 2004;109:320-323.)

Key Words: peripheral vascular disease ■ kidney ■ creatinine

It is increasingly accepted that mild to moderate chronic renal insufficiency is a risk factor for cardiovascular disease. However, most studies of cardiovascular disease in patients with chronic renal insufficiency have not examined lower-extremity peripheral arterial disease (PAD), and disease prevalence has only been described in a few select groups of patients with renal insufficiency. Because PAD is highly prevalent among dialysis patients, as evidenced by the exceedingly high amputation rates in this group, we hypothesize that there is also a high prevalence of PAD among the much larger number of persons with chronic renal insufficiency. We used ankle-brachial index (ABI) measurements from the National Health and Nutrition Examination Survey (NHANES) 1999 to 2000 to test this hypothesis.

Methods

Data Sources

Since the early 1960s, the National Center for Health Statistics has conducted a series of cross-sectional national surveys of the noninstitutionalized civilian population. In each survey, the population was sampled with a complex, stratified, multistage probability cluster sampling design to provide data that are representative of the overall United States population. Beginning in 1999, NHANES became a continuous survey, and NHANES 1999 to 2000 refers to the first 2 years of data for the now ongoing NHANES. As for the prior NHANES, NHANES 1999 to 2000 involved collection of interview, examination, and laboratory data. However, unlike prior surveys, the present survey included a detailed lower-extremity examination that involved ABI measurement, a noninvasive measure of lower-extremity atherosclerosis. It is thus possible to use NHANES 1999 to 2000 data to estimate the prevalence and correlates of PAD as indicated by a low ABI. More detailed information on survey design and procedures is available at http://www.cdc.gov/nchs/about/major/nhanes/NHANESHIII_Reference_Manuals.htm.

ABI Measurements

Briefly, study participants ≥40 years old were invited to undergo lower-extremity examination. Persons with bilateral amputations or weighing more than 400 pounds were excluded. Supine systolic pressure was measured in 1 arm (brachial artery) and both ankles (posterior tibial arteries). The ABI was calculated by dividing the mean systolic blood pressure in the arm by the mean systolic blood pressure in the respective ankle. For the purposes of this analysis, the lowest ABI obtained for either leg was taken as the ABI measurement for that patient. Details of the ABI measurement procedure in NHANES 1999 to 2000 are available at http://www.cdc.gov/nchs/data/nhanes/frequency/lexabdoc.pdf.
TABLE 1. Population Characteristics by Level of Renal Function From NHANES 1999–2000

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CRCL &gt;60 mL·min⁻¹·1.73 m⁻² (n=2018)</th>
<th>CRCL &lt;60 mL·min⁻¹·1.73 m⁻² (n=211)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>55.1 (±0.4)</td>
<td>76.1 (±1.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% Female</td>
<td>52.2±0.7</td>
<td>48.6±5.0</td>
<td>0.48</td>
</tr>
<tr>
<td>% Black</td>
<td>8.4±0.6</td>
<td>10.0±1.9</td>
<td>0.34</td>
</tr>
<tr>
<td>Comorbid conditions, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>7.9±0.9</td>
<td>13.6±2.8</td>
<td>0.035</td>
</tr>
<tr>
<td>Insulin users</td>
<td>1.9±0.5</td>
<td>7.6±2.4</td>
<td>0.021</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>1.6±0.4</td>
<td>6.8±2.4</td>
<td>0.034</td>
</tr>
<tr>
<td>Glycosylated hemoglobin</td>
<td>5.6±0.04</td>
<td>5.9±0.08</td>
<td>0.002</td>
</tr>
<tr>
<td>Smoking (ever vs never)</td>
<td>54.6±1.4</td>
<td>56.5±4.7</td>
<td>0.72</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>8.7±0.8</td>
<td>29.0±3.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke history</td>
<td>2.8±0.5</td>
<td>12.4±3.2</td>
<td>0.01</td>
</tr>
<tr>
<td>Hypertension</td>
<td>33.±1.4</td>
<td>57.3±4.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>213.8±1.3</td>
<td>209.9±2.8</td>
<td>0.16</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.3±0.3</td>
<td>26.2±0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean systolic blood pressure, mm Hg</td>
<td>127.3±0.8</td>
<td>144.3±2.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean diastolic blood pressure mm Hg</td>
<td>74.6±0.4</td>
<td>68.4±1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ABI, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABI &gt;1.3</td>
<td>3.4±0.7 (n=72)</td>
<td>3.7±0.2 (n=9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1.0&lt;ABI&lt;1.3</td>
<td>86.2±1.1 (n=1674)</td>
<td>60.9±4.4 (n=121)</td>
<td></td>
</tr>
<tr>
<td>0.9&lt;ABI&lt;1.0</td>
<td>6.7±0.6 (n=165)</td>
<td>14.1±2.9 (n=31)</td>
<td></td>
</tr>
<tr>
<td>ABI &lt;0.9</td>
<td>3.7±0.5 (n=107)</td>
<td>24.0±4.5 (n=50)</td>
<td></td>
</tr>
</tbody>
</table>

n indicates sample number of NHANES participants. Data are mean or percent ± SE.
P values are χ² test for categorical variables and t test for continuous variables. All values were calculated with the examination weight variable (WTMEC2YR).

Estimation of Creatinine Clearance

We used the Cockcroft-Gault formula standardized to body surface area to estimate creatinine clearance (CRCL). For the purposes of this analysis, subjects were considered to have renal insufficiency if their estimated CRCL was <60 mL·min⁻¹·1.73 m⁻². All analyses compare this group with the reference group of persons with estimated CRCL ≥60 mL·min⁻¹·1.73 m⁻².

Covariates

Self-reported race was defined as non-Hispanic black versus all other. Determination of comorbid conditions (diabetes, insulin use, diabetic retinopathy, hypertension, coronary artery disease, stroke history, and smoking history) was based on patient interview responses. In addition, body mass index (BMI), the average of 4 measurements of systolic and diastolic blood pressure, glycosylated hemoglobin, and total cholesterol measurements were included in multivariable analysis.

Statistical Analysis

Sampling weights are provided with NHANES 1999 to 2000 data. These take into account the unequal probabilities of selection that result from the sample design, from nonresponse, and from planned oversampling of certain subgroups. Standard errors were calculated by the recommended jackknife method (http://www.cdc.gov/nchs/data/nhanes/guidelines1.pdf) with SAS-callable SUDAAN version 8 software (Research Triangle Park). Differences in continuous variables between renal function categories were compared with a t test, and differences in categorical variables were measured with a χ² test. We developed a categorical variable for ABI that adhered to conventional ABI cutoff points (ie, ABI <0.9, 0.9 to 0.99, 1.0 to 1.3, and >1.3). PAD is defined as an ABI <0.9, and values between 1.0 and 1.3 are considered normal. An ABI of 1.0 to 1.3 served as the referent category for all logistic regression analyses. We measured the association of the categorical ABI variable with renal insufficiency using univariate logistic regression analysis for which the outcome was estimated CRCL <60 versus ≥60 mL·min⁻¹·1.73 m⁻². We then developed multivariate logistic regression models to adjust sequentially for confounders including demographic (age, gender, and race) and clinical characteristics (diabetes, insulin use, retinopathy, coronary artery disease, stroke history, cholesterol, glycosylated hemoglobin, smoking history, BMI, hypertension history, and blood pressure measurements).

Results

ABI was recorded for at least 1 leg in 2381 (83%) of the 2875 lower-extremity examination participants. Serum creatinine was measured in 2233 of these participants. Four participants were excluded because they were missing weight data, and we were therefore unable to estimate CRCL. The study sample thus consisted of 2229 persons with ABI and CRCL data. Among these, 211 had an estimated CRCL <60 mL·min⁻¹·1.73 m⁻² (a projected 5.8±0.7% of the noninstitutionalized civilian population more than 40 years old, or 5.0±0.6 million persons). Table 1 describes the characteristics of the study sample extrapolated to the US population. A substantially higher percentage of persons with renal insufficiency were in the low ABI categories (<0.9 and 0.9 to 0.99) compared with those with CRCL ≥60 mL·min⁻¹·1.73 m⁻². However, those with renal insufficiency were on average older; had a higher prevalence of diabetes, coronary artery disease, stroke, and hypertension; had higher mean glycosylated hemoglobin, smoking history, BMI, hypertension history, and blood pressure measurements).
The present study demonstrates a remarkably high prevalence of PAD (defined as an ABI <0.9) among a representative sample of the US population ≥40 years old with renal insufficiency. On the basis of these data, an estimated 24% of the US population ≥40 years old with an estimated CRCL <60 ml·min⁻¹·1.73 m⁻² have PAD. Even after adjustment for important confounders such as age, diabetes, diabetes severity, and coronary artery and cerebrovascular disease, persons with renal insufficiency are still more than twice as likely to have an ABI <0.9 as persons with a CRCL ≥60 ml·min⁻¹·1.73 m⁻².

Discussion

The high unadjusted association of renal insufficiency with low ABI reflects, to a large extent, the older age of the renal insufficiency group. A high prevalence in this group of other established cardiovascular risk factors such as diabetes and hypertension, in addition to a high prevalence of existing coronary artery and cerebrovascular disease, also contributes to the high unadjusted association of renal insufficiency with low ABI. Several traditional cardiovascular risk factors, such as cholesterol and smoking, are no more prevalent among persons with renal insufficiency than among those with normal renal function and thus do not appear to explain the cross-sectional association seen here between ABI and renal insufficiency.

There are several possible explanations for the high adjusted association of renal insufficiency with low ABI. One possibility is that renal insufficiency may be a marker for more generalized atherosclerosis. In support of this, the presence of baseline cardiovascular disease is independently associated with progression to end-stage renal disease among patients with chronic kidney disease.14 Alternatively, there may be a causal association between renal insufficiency and progression of lower-extremity atherosclerosis. Potential pathophysiological mechanisms by which decreased CRCL itself might predispose to PAD include altered calcium-phosphorus, homocysteine, and lipoprotein(a) metabolism and alterations in inflammatory and coagulation pathways.9

Table 2 shows the results of both univariate and multivariable logistic regression analyses. Univariate logistic regression analysis shows that compared with their counterparts with CRCL ≥60 ml·min⁻¹·1.73 m⁻², persons with reduced renal insufficiency were more than 9-fold more likely to have an ABI <0.9 (versus an ABI of 1 to 1.3). We developed 2 multivariable models to adjust sequentially for demographic characteristics and comorbid conditions that might confound the association between renal insufficiency and ABI. After adjustment for age, gender, and race, renal insufficiency remained strongly associated with an ABI <0.9 (OR 3.0, 95% CI 1.7 to 5.3, P ≤ 0.001). This association persisted after further adjustment for comorbid conditions including diabetes, coronary artery disease, and history of stroke; measures of diabetes severity (glycosylated hemoglobin, self-reported retinopathy, and insulin use); history of diagnosed hypertension; and measured blood pressure, total cholesterol, BMI, and smoking history (ABI <0.9; OR 2.5, 95% CI 1.2 to 5.1, P = 0.011, referent category ABI 1.0 to 1.3).

Relative to methods for detecting other forms of cardiovascular disease (eg, cardiac stress testing), ABI measurement is a simple, noninvasive procedure that can be performed easily in the outpatient setting.15 Routine ABI measurement could be used to identify patients with subclinical PAD who might benefit from educational and therapeutic interventions for PAD. Early identification of PAD before progression to advanced ischemia may be particularly important in patients with renal insufficiency, given data showing that patients with renal insufficiency who undergo lower-extremity bypass are more likely than those with normal renal function to present with gangrene and ischemic ulceration at the time of surgery and to experience postoperative death and cardiovascular complications.19

In addition, because of the well-documented association of low ABI with cardiovascular mortality, ABI measurement could also help to target patients at highest risk for cardiovascular death as candidates for secondary prevention efforts. The present results show that self-reported history of coronary artery disease is an insensitive predictor of low ABI in patients with renal insufficiency. Thus, measurement of ABI...
in patients with renal insufficiency could contribute valuable information on cardiac risk beyond what is supplied by the medical history alone.

NHANES provides nationally representative data and overcomes many problems of sampling bias, but the present findings must be interpreted in the context of the study design. Specifically, it is unclear from these cross-sectional data whether renal insufficiency is a true causal “risk factor” for the development of PAD. Although renal insufficiency does appear to be associated with the future development of claudication, further studies are needed to measure the association of baseline renal insufficiency with progression of PAD and future PAD events. A second concern is that the present analysis may underestimate the prevalence of PAD in persons with renal insufficiency because of the high prevalence of vascular calcification in this group, leading to falsely elevated ABIs. In this situation, a toe brachial index may be a more accurate screening test for PAD. We are unable to overcome this limitation because toe pressures were not measured in NHANES 1999 to 2000.

Conclusions

PAD is remarkably common in persons with renal insufficiency, and there is an independent cross-sectional association between PAD and renal insufficiency. In the primary care setting, the combination of accurate diagnosis of renal insufficiency (either via measurement or estimation of CRCL or via estimation of glomerular filtration rate) and routine ABI measurement in this group would facilitate more efficient identification of patients with subclinical PAD, a group most likely to benefit from PAD-specific educational interventions and therapy and also from more general cardiovascular risk-reduction efforts.

Acknowledgments

Dr O’Hare is supported by a Health Services Research Career Development Award from the Department of Veterans Affairs. Dr Hsu is funded by the National Institutes of Health (DK 61520).

References

High Prevalence of Peripheral Arterial Disease in Persons With Renal Insufficiency: Results From the National Health and Nutrition Examination Survey 1999–2000
Ann M. O’Hare, David V. Glidden, Caroline S. Fox and Chi-yuan Hsu

Circulation. 2004;109:320-323; originally published online January 19, 2004; doi: 10.1161/01.CIR.0000114519.75433.DD
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/109/3/320

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/