Relationship between Ankle-Brachial Index and Chronic Kidney Disease in Hypertensive Patients with No Known Cardiovascular Disease

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Both decreased GFR and albuminuria are associated with an elevated prevalence of peripheral artery disease. However, the combined effects of these alterations previously were not evaluated. Patients with hypertension and with no known vascular disease (n = 955; mean age 66 y; 56% male) were selected from internal medicine outpatient clinics throughout Spain. Cardiovascular risk factors, urinary albumin excretion, and the ankle-brachial index (ABI) were assessed in all participants. GFR was estimated according to the Cockcroft-Gault equation. Of the study population, 62% had diabetes, 23.8% had a GFR <60 ml/min per 1.73 m², and 43.8% had albuminuria. The prevalence of ABI <0.9 was 45.7%. Multivariate analysis indicated that the factors that were associated independently with low ABI were age (odds ratio [OR] 1.06; 95% confidence interval [CI] 1.03 to 1.08; P < 0.0001), triglyceride concentration (OR 1.003; 95% CI 1.001 to 1.005; P < 0.012), smoking habit (OR 1.72; 95% CI 1.13 to 2.63; P = 0.012), and a GFR <60 ml/min per 1.73 m² (OR 1.47; 95% CI 1.01 to 2.17; P = 0.049). In patients with hypertension and without known vascular disease, reduced GFR and albuminuria are associated independently with an ABI <0.9. Their combined presence characterizes a subgroup of the population who have an elevated prevalence of peripheral artery disease and could benefit from early diagnosis and treatment.


Patients with peripheral artery disease (PAD) of the lower limbs, whether symptomatic or not, have an elevated risk for cardiovascular disease and premature death (1,2). Early detection of PAD identifies a group of patients who would benefit from aggressive cardiovascular risk factor modification and from antiplatelet therapy. Several factors have been associated with the development of PAD, among which are age, gender, diabetes, smoking habit, dyslipidemia, and hypertension. High BP is an important risk factor in the progressive deterioration of renal function and in the development of albuminuria, particularly in patients of advanced age. Although both a decreased GFR (3–7) and the presence of albuminuria (8,9) have been associated independently with an elevated prevalence of PAD, their combined effects were not evaluated previously. This is of considerable importance given that not only PAD but also chronic renal disease is additive, and both are independent risk factors for the development of cardiovascular disease (10,11). Their simultaneous presence characterizes a subgroup of patients who have very high risk for cardiovascular disease and could benefit from early diagnosis and treatment (12). The objective of the present study was to determine the association between the GFR and albuminuria with the presence of subclinical PAD of the lower limbs in a large population of hypertensive patients with no known cardiovascular disease.

Materials and Methods

Patients

Participants in the Modificacion de le Estratificacio¨n del Riesgo con el Indice Tobillo-brazo (MERITO) study were of both genders, were between the ages of 50 and 85 yr, and attended internal medicine outpatient clinics in hospitals throughout Spain. Each investigator was required to measure the ankle-brachial index (ABI) in 20 consecutive patients who attended the clinic; 10 had type 2 diabetes, and 10 did not have diabetes but had a risk for death from cardiovascular disease ≥3% over the next 10 yr, calculated according to the equation of the System-
atic Coronary Risk Evaluation (SCORE) Project for low-risk countries (13). The diagnosis of hypertension required that the patient had had such a diagnosis made previously by the treating physician, a BP \( \geq 140/90 \) mmHg in patients without diabetes or \( \geq 130/80 \) mmHg in patients with diabetes recorded on two separate occasions, or treatment with antihypertensive drugs. Of the participants in the MERITO study, 85% were hypertensive and were selected for the current study. The diagnosis of diabetes was established in accordance with the criteria of the American Diabetes Association (14). All individuals with a definitive or suspected diagnosis of vascular disease, including coronary, cerebral, or PAD, were excluded from the study.

On entry into the study, a clinical history was taken and a thorough physical examination was made. Fasting venous blood was taken for biochemical analyses. Plasma concentrations of glucose, glycated hemoglobin, creatinine, lipids, and lipoproteins were measured using standardized biochemical methods. Estimated creatinine clearance was calculated by the Cockroft-Gault equation standardized to body surface area (15). Urinary albumin excretion was estimated using one or more of the following methods: Quantification of 24-h albumin excretion (54.8% of study patients), albumin-to-creatinine ratio on a spot urine specimen (36.5% of study patients), or quantification of albumin in an overnight sample (8.6% of study patients). Albuminuria was present when the albumin-to-creatinine ratio was \( >30 \) mg/g, the 24-h albumin excretion was \( >30 \) mg/24 h, or the concentration of albumin in the overnight sample was \( >20 \) mg/min.

The ABI was determined with a bidirectional portable echo-Doppler of 8 MHz (Mini Doppler HADECO ES-100, Kawasaki, Japan) and a calibrated mercury sphygmomanometer. The systolic BP (SBP) was measured in the posterior tibial and pedal arteries of both lower limbs and the brachial arteries of both upper limbs. The value of the ABI was calculated using the greater SBP obtained in the lower limbs divided by the lowest ABI obtained for each patient was used in the subsequent statistical analyses. A value of ABI \( <0.9 \) was considered pathologically low. All patients gave written informed consent, and the study was approved by the Committee on Ethics and Research of the Hospital Ramón y Cajal in Madrid.

**Table 1. Characteristics of the study population as a function of creatinine clearance**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Creatinine Clearance</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(&lt;60 \text{ ml/min per 1.73 m}^2)( (n = 227; 23.8%)</td>
<td>(\geq60 \text{ ml/min per 1.73 m}^2)( (n = 728; 76.2%)</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>41</td>
<td>61</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>71.8 (6.5)</td>
<td>64.2 (7.7)</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>28.8 (5)</td>
<td>30.9 (5)</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>11.1</td>
<td>24.5</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>63.4</td>
<td>62.3</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>151 (24)</td>
<td>150 (19)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>79 (12)</td>
<td>85 (11)</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>123 (41)</td>
<td>135 (40)</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>54 (29)</td>
<td>51 (20)</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>154 (98)</td>
<td>166 (106)</td>
</tr>
<tr>
<td>GFR (ml/min per 1.73 m(^2))</td>
<td>46.4 (10.5)</td>
<td>92.2 (27.6)</td>
</tr>
<tr>
<td>Antihypertension treatment (%)</td>
<td>91.6</td>
<td>82.4</td>
</tr>
<tr>
<td>Hypolipemic treatment (%)</td>
<td>61.9</td>
<td>65.8</td>
</tr>
<tr>
<td>Albuminuria (%)</td>
<td>51.1</td>
<td>41.5</td>
</tr>
<tr>
<td>ABI (&lt;0.9)</td>
<td>37.4</td>
<td>24.3</td>
</tr>
</tbody>
</table>

*ABI, ankle-brachial index; DBP, diastolic BP; SBP, systolic BP.*

**Statistical Analyses**

The quantitative variables are presented as the mean (SD), and the qualitative variables are presented as percentages. The comparisons between the quantitative variables were with the \( t \) test, and the comparisons between the qualitative variables were with the \( \chi^2 \) test. To evaluate the independent association between ABI (dependent variable) and renal disease, we performed logistic regression analyses in which the independent variables such as age, gender, and classical risk factors all were entered into the model. Statistic software program used for all analyses was the SAS package (version 8.2; SAS Institute, Cary, NC).

**Results**

There were 955 white patients included in the study, 56% were male, and the overall mean age was 66 yr (8.1). Of these, 62% had diabetes, 21% were current smokers, 85% were receiving antihypertensive treatment, and 65% were receiving hypolipemic agents. Of the participants, 34.3% had a creatinine clearance \( >90 \) ml/min per 1.73 m\(^2\), 41.9% had a mildly decreased GFR (between 60 and 89 ml/min per 1.73 m\(^2\)), 21.8% had a moderately decreased GFR (between 30 and 59 ml/min per 1.73 m\(^2\)), and 2% had a severely decreased GFR (\(<30 \) ml/min per 1.73 m\(^2\)). Albuminuria was noted in 43.8% of patients. Patients without diabetes had a poorer risk profile. They were older and had a greater proportion of cardiovascular disease risk factors. However, the percentage of those with albuminuria and/or a decreased GFR did not differ between patients with and without diabetes (data not shown). The mean ABI of the overall population was 0.97 (0.16); 27.4% of the participants had an ABI \(<0.9\), 22.6% between 0.7 and 0.9, and 4.7% between 0.4 and 0.7, and only one participant had an ABI \(<0.4\).

The patients with a GFR \(<60 \) ml/min per 1.73 m\(^2\) (Table 1) were predominantly female, older, and on antihypertensive...
treatment. Conversely, body mass index, diastolic BP and LDL cholesterol were lower, and there was a lower prevalence of smoking habit. Also, the presence of albuminuria was greater in these patients with a decreased GFR (51.1 versus 41.5%; P = 0.007).

The percentage of patients with low ABI was greater among participants with a GFR <60 ml/min per 1.73 m² (37.4 versus 24.3%; P < 0.0001), with a significant positive correlation between the GFR and the ABI (r = 0.097, P = 0.003). The prevalence of ABI <0.9 as a function of the grade of deterioration of the GFR can be seen in Table 2: The lower the GFR, the higher the prevalence of PAD. The patients with albuminuria had, as well, a greater prevalence of low ABI (32.2 versus 23.3%; P = 0.001).

We performed multivariate analysis to assess the factors that were related to a low ABI. The continuous variables that were included in the model were age in years; body mass index in kg/m²; and LDL cholesterol, HDL cholesterol, and triglycerides in mg/dl. The categorical variables were gender, current smoking, and presence or absence of diabetes, hypertension, and chronic renal disease, particularly in patients with hypercholesterolemia.

The prevalence of a low ABI in patients who had a GFR ≥60 ml/min per 1.73 m² and did not have albuminuria was 21.8%; and in patients who had only a GFR <60 ml/min per 1.73 m², the prevalence was 27.2%; in patients with only albuminuria, the prevalence was 28.8%; and in patients with both a GFR <60 ml/min per 1.73 m² and albuminuria, the prevalence was 45.7% (P < 0.001; Figure 1).

Discussion

Although the presence of chronic kidney disease, either as reduction in the GFR or as albuminuria, was shown previously to be associated independently with the risk for PAD (3–6), cardiovascular disease, and premature death (3,16–19), the combined effects of small decreases in GFR and albuminuria were not evaluated previously in relation to arteriosclerosis of the lower limbs. Our present data, obtained in a population of patients with hypertension and with no known cardiovascular disease, demonstrated that a GFR <60 ml/min per 1.73 m² and the presence of albuminuria both were associated with a reduced ABI and that these relationships were independent of other classical risk factors of cardiovascular disease. More than one quarter of the participants with a reduced GFR or with albuminuria had a low ABI, and this prevalence increased up to 50% in the group of patients with both disorders. The percentage of patients with a low ABI increased with decreasing GFR, and this was apparent even in patients with a modest reduction in renal function.

Our results are useful because they enable the identification of a section of the population with a high prevalence of PAD and, as such, with an elevated risk for developing coronary artery disease, cerebrovascular disease, or premature death. This elevated prevalence would justify the recommendation to perform an ABI measurement in patients with a reduced GFR and/or albuminuria so that if a low ABI is recorded, then aggressive measures of secondary prevention of cardiovascular disease can be implemented. Given the additive and independent cardiovascular disease risk that is conferred by both PAD and chronic renal disease, particularly in patients with hypertension (11), further studies would be warranted to determine the combined effect of chronic kidney disease and albuminuria.

Table 2. OR (95% CI) for an ABI <0.9 segregated with respect to GFR

<table>
<thead>
<tr>
<th>Estimated Creatinine Clearance Rate</th>
<th>Crude OR</th>
<th>Age- and Gender- Adjusted OR</th>
<th>Fully Adjusted Modelb OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;90 ml/min per 1.73 m²</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>60 to 89 ml/min per 1.73 m²</td>
<td>1.39 (0.98 to 1.96)</td>
<td>1.16 (0.80 to 1.67)</td>
<td>1.17 (0.78 to 1.77)</td>
</tr>
<tr>
<td>30 to 59 ml/min per 1.73 m²</td>
<td>2.12 (1.44 to 3.12)</td>
<td>1.57 (1.01 to 1.44)</td>
<td>1.71 (1.02 to 2.86)</td>
</tr>
<tr>
<td>&lt;30 ml/min per 1.73 m²</td>
<td>4.17 (1.63 to 10.67)</td>
<td>2.89 (1.08 to 7.73)</td>
<td>1.75 (0.55 to 5.57)</td>
</tr>
</tbody>
</table>

aCI, confidence interval; OR, odds ratio.
bThe continuous variables that were included in the model were age in years; body mass index in kg/m²; and LDL cholesterol, HDL cholesterol, and triglycerides in mg/dl. The categorical variables that were included in the model were gender, current smoking, and presence or absence of diabetes.
the efficacy of recommending a routine evaluation of the presence of atherosclerosis in other vascular beds in these patients. Several mechanisms can be hypothesized to explain the association between a reduction in GFR and vascular disease. Despite that the two entities have risk factors in common, our results indicate that the relationship is independent of the presence of other classical risk factors. In patients with diabetes and a reduced GFR and without albuminuria, the underlying cause of the renal insufficiency could be the presence of atherosclerosis in the renal artery or in arteries of narrow diameter (20). Other factors that are present in patients with chronic kidney disease, such as hyperhomocysteinemia, increase in inflammation activity, oxidative stress, and endothelial dysfunction, also could underlie the higher prevalence of PAD in patients with impaired renal function. Factors that link albuminuria to vascular disease have not been ascertained unambiguously. Albuminuria seems to identify individuals with generalized endothelial dysfunction and also may be a marker of a prothrombotic state (21,22). What is clear, however, is that it acts as a risk factor that is independent of renal function. Our present results demonstrate that low GFR and albuminuria are alterations that are associated independently with a low ABI, suggesting that the underlying routes of their association with vascular disease may be different.

In our study, reduced GFR was highly prevalent as a result of the advanced age of the patients, of all participants’ having hypertension, and of there being an elevated prevalence of diabetes. These observations coincide with other data that have been published on similar populations (23).

Our study has several limitations. The number of participants is relatively small in epidemiologic terms, which suggests that there may not have been sufficient numbers of patients representing the whole range of renal function deterioration. Other shortcomings of the study are that the albuminuria was measured using only one sample of urine, that a urinary sedimentation analysis was not performed simultaneously, and that the analyses were not conducted centrally. Nevertheless, all of these limitations would have served to reduce the possibilities of finding significant associations.

Conclusion
Our data indicate that both a reduction in the GFR and albuminuria are independent as well as additive factors for the presence of subclinical PAD in hypertensive patients with no known cardiovascular disease. Given our findings of an elevated prevalence of PAD in asymptomatic patients with an estimated creatinine clearance <60 ml/min per 1.73 m² and with albuminuria, we suggest that routine measurement of ABI be performed in these patients to identify individuals who are at very high risk and would benefit from the early implementation of appropriate therapeutic strategies.

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