Relationship between kidney function and risk of asymptomatic peripheral arterial disease in elderly subjects

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Abstract

Background. Limited data exist regarding the relationship between kidney function and incident asymptomatic peripheral arterial disease (PAD).

Methods. The study population consisted of 2881 participants of the Intervention Project on Cerebrovascular Diseases and Dementia in the Community of Ebersberg, Bavaria, a community-based cohort of elderly individuals. Kidney function was calculated as creatinine clearance (Ccr) estimated by the Cockcroft–Gault formula. Incident PAD was defined as a new onset of ankle-brachial index <0.9 assessed at regular examinations among those with an ankle brachial pressure index (ABPI) ≥0.9 at baseline. Relative risks (RR) for PAD were compared across declining kidney function quartiles.

Results. Mean serum concentration of creatinine and Ccr were 0.82 ± 0.31 mg/dL and 78 ± 21 mL/min/1.73 m². After 6 years of follow-up, 478 (17%) participants developed incident asymptomatic PAD. After adjustment for demographic factors and cardiovascular risk factors, lower Ccr quartiles were directly associated with a higher risk of PAD. Compared with participants in quartile 1 (≥89 mL/min/1.73 m²), the adjusted RR (95% CI) for PAD were 1.01 (0.88–1.19) for quartile 2 (75–89 mL/min/1.73 m²), 1.05 (0.93–1.23) for quartile 3 (64–75 mL/min/1.73 m²) and 1.10 (1.01–1.44) for quartile 4 (<64 mL/min/1.73 m²; P = 0.009 for trend). Cardiovascular events as a function of baseline Ccr and incident PAD showed that most vascular events occurred in participants with Ccr <60 mL/min/1.73 m² at baseline and incident PAD (log-rank test, P = 0.0018).

Conclusions. Lower kidney function is associated with incident asymptomatic PAD. In addition, the combination of impaired kidney function and incident PAD better predicts cardiovascular outcomes.

Keywords: ankle-brachial index; cardiovascular disease; chronic kidney disease; kidney function; peripheral vascular disease

Introduction

The leading cause of death in patients with chronic kidney disease (CKD) is cardiovascular disease (CVD) [1]. Up to 50% of patients on chronic dialysis die of cardiovascular events with a mortality rate of 15–30 times higher than that of age-adjusted controls [2,3]. Increasing evidence has revealed that this cardiovascular risk is not just limited to end-stage kidney disease patients but appears to be also directly related to kidney disease progression [1,3–8]. Go et al. observed in a large community-based population a stepwise increase in risk for all-cause mortality and cardiovascular events with worsening kidney disease [1]. Furthermore, a recent study by Russo et al. demonstrated that patients with CKD have an increased incidence of coronary artery vascular disease with 40% of patients having evidence of coronary calcification compared to 13% in matched controls [9]. Thus, vascular disease appears to begin in the predialysis period.

Several factors are felt to lead to increased vascular disease in patients with kidney disease including traditional risk factors such as diabetes mellitus, hypertension and tobacco abuse. Endothelial dysfunction, low-grade inflammation, dyslipidaemia and abnormal mineral metabolism have also been shown to contribute to increased atherosclerosis in these patients [9–13]. Despite the extensive evidence demonstrating the increased risk of coronary artery disease, the association between CKD and the development of asymptomatic peripheral arterial disease (PAD) has been less studied. To date, only one longitudinal study of middle-aged community-based patients has noted an association between kidney disease progression and symptomatic incident PAD [14]. Consequently, the relationship between kidney function levels and asymptomatic incident PAD in the elderly remains unknown. Furthermore, the association between different levels of kidney function, asymptomatic incident PAD and cardiovascular outcomes has not been fully investigated.

In the current investigation from the INVADE (Intervention Project on Cerebrovascular Diseases and Dementia in the Community of Ebersberg, Bavaria) study, we evaluated (i) incidence of new asymptomatic cases of PAD in patients across kidney function levels and (ii) the relationship between kidney function at baseline, incident asymptomatic PAD and vascular events during the follow-up period.
Materials and methods

Subjects

The design of the INVADE study has been described previously [15]. This prospective population-based cohort included a total of 3364 patients from Ebersberg, Germany. All members of this community that were born before 1946 and were a member of the health insurance company, AOK (Allgemeine Ortskrankenkasse), were eligible to participate in this investigation. Thus, ~40% of the population of Ebersberg was eligible \( n = 10325 \). A total of 3905 participants followed up the invitation during the baseline phase from 2001 to 2003, of whom 3364 were included in the present study. The remaining subjects were excluded due to incomplete data collection. Compared to those excluded, demographics and event rates were similar among subjects who were retained in this analysis (not shown). A group of primary care physicians in Ebersberg performed the original baseline data collection on the participants. These data included history and physical examination, standardized questionnaire, overnight fasting venous blood sample for baseline laboratories, 12-lead electrocardiogram and ankle-brachial index (ABI) assessment according to a standardized protocol. Participants were followed at 2-year intervals for reassessment of the same tests by this same group of physicians. A complete follow-up evaluation was performed at the end of the 6-year follow-up. The local institutional review board approved this investigation and all patients signed informed consent prior to enrolling into the study.

Study variables

The primary independent variable of interest was kidney function. We used the Cockcroft–Gault formula to measure creatinine clearance (Ccr), which includes measures of age, weight and sex, and was standardized for body surface area using the Dubois formula [16,17]. We elected to evaluate quartiles of Ccr as our primary predictor variable. CKD was defined as Ccr < 60 mL/min/1.73 m². Of note, the Cockcroft–Gault prediction equation has been used in other analyses of the INVADE study [18,19] and has been validated in older European adults [20,21]. Nonetheless, we have repeated our analysis using the four-variable abbreviated Modified Diet Renal Disease study equation [22] which provided similar results and is not described further.

The primary dependent variable of interest was asymptomatic incident PAD as estimated by ABI. The systolic blood pressure of the posterior tibial artery was measured in the supine position on both sides with an 8-MHz continuous-wave Doppler probe and a random-zero sphygmonanometer. Blood pressure of both arms was measured twice with a random-zero sphygmonanometer and averaged. The ABI was calculated by dividing the ankle systolic pressure by the higher of the two brachial pressures. For analysis, we used the lowest ABI. The normal range for ABI is from 1.0 to 1.3. PAD was defined as an ABPI < 0.9 in either leg based on prior studies [23]. Of note, all participants diagnosed with PAD were asymptomatic during the history and physical examination performed at a 2-year interval and at the end of the follow-up period.

In this analysis, we used the same cardiovascular endpoints specified by the original INVADE study. The endpoints were the occurrence of cardiovascular events defined as a composite of myocardial infarction, stroke and vascular death. Once subjects entered the INVADE study, they were continuously monitored for major cardiovascular events through linkage of the study database with the 3-month visit files from the primary care physicians, the AOK database and the municipality. If an event was reported, additional information was obtained through hospital records, autopsy records and death certificates. Two physicians (D.S. or T.E.) independently coded all fatal and non-fatal events.

Baseline characteristics

Enrolled participants completed a standardized computerized questionnaire at the onset of the investigation which provided information on current health status, medical history, body mass index, smoking status and number of pack-years, actual medication use and cardiovascular risk factors. These risk factors include: prevalence of ischaemic heart disease (documented by previous myocardial infarction or angina pectoris, bypass surgery or > 50% angiographic stenosis of ≥ 1 major coronary artery), prevalence of stroke (neurological deficit that persisted longer than 24 h, evaluated by a neurologist), prevalence of diabetes mellitus (treatment with anti-diabetic drugs or overnight fasting serum glucose levels ≥ 126 mg/dL) and prevalence of arterial hypertension (treatment with anti-hypertensive medication or documented blood pressure ≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic measured in a standardized fashion).

Overnight fasting blood samples were drawn from each subject and were transferred on ice to a central laboratory that performed all analyses. Serum creatinine was measured by a kinetic alkaline picrate (Jaffe) method [24]. We used a high sensitivity assay for measurement of serum high sensitivity C-reactive protein (N High Sensitivity CRP, DADE Behring, Germany) with a lower detection level of 0.175 mg/l and a coefficient of variation of 7.6%. Glycosylated haemoglobin (HbA1c) was measured by high-pressure liquid chromatography separation of haemoglobin fractions with a reference value of 4.0–6.0% and a coefficient of variation of 1.8% on a Hitachi 8100 A 0-180 instrument (KDK). Levels of total homocysteine were measured by high-performance liquid chromatography with fluorescence detection [25]. The fasting blood samples were collected into ethylenediaminetetraacetic acid (EDTA) tubes containing 3-deazaneplanocin A (100 mmol/L) [26]. In these tubes, homocysteine remained stable up to 72 h after sampling. All analyses were performed in duplicate and the mean value was taken. The intra- and inter-assay precision was 1.6–3.0% and 1.9–4.4%, respectively, after 5 weeks. In addition to these values, cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides and fasting serum glucose were measured.

Statistical analysis

All values are given as mean and standard deviation (SD) or as counts and percentages. We used chi-square tests, independent t-tests, Mann–Whitney U-tests and the Spearman rank correlation for univariate analysis where appropriate. Multivariate Cox regression was used to analyse the association between baseline kidney function and development of PAD. To examine the association between kidney function, new onset PAD and cardiovascular events at the end of the follow-up period, the whole cohort was divided in four groups on the basis of CKD status at baseline and incident PAD. These relationships were calculated using Kaplan–Meier analysis and Cox proportional hazard regression. All multivariable analyses were adjusted for the same relevant covariates age, sex, body mass index, smoking, prevalent ischaemic heart disease, systolic blood pressure, diastolic blood pressure, anti-hypertensive medications, statin administration, aspirin usage, LDL-C, HDL-C triglycerides, HbA1c, hs-C-reactive protein and homocysteine to ensure giving an unbiased estimate for the relation between baseline kidney function and asymptomatic incident PAD. Calculations were performed with JMP 5.0.1 software (SPPS Inc.). A calculated difference of \( P < 0.05 \) was considered to be statistically significant.

Results

Baseline characteristics

Of the 3364 participants included in the analytic cohort, a total of 483 (14%) subjects had PAD at baseline defined as an ABI ≤ 0.9 and from the remaining 2881 subjects, 478 (17%) subjects developed PAD defined as an ABI < 0.9 during the 6 years of follow-up. Of the 2881 subjects, the mean serum creatinine and Ccr were 0.82 ± 0.31 mg/dL and 78 ± 21 ml/min/1.73 m². Of note, 490 (17%) participants had CKD defined as Ccr < 60 ml/min/1.73 m² at the initiation of the study. Most participants with CKD had moderate kidney disease: 11 (0.4%) had a Ccr < 30 ml/min/1.73 m², 85 (3%) had a Ccr 30–44 ml/min/1.73 m² and 394 (13.7%) of participants had a Ccr 45–60 ml/min/1.73 m². The characteristics of these participants with and without asymptomatic PAD at close out are shown in Table 1. Participants that developed new PAD were older, smokers and had a higher prevalence of hypertension, ischaemic heart disease and stroke. These participants also had a slightly lower kidney function at baseline. Of note, partici-
pants who did not develop PAD during the course of the study were more likely to be diabetic and less likely to be receiving a statin. The mean ABI at the end of the follow-up period among participants who developed PAD was 0.73 ± 0.22.

**Longitudinal association between baseline kidney function and incident PAD**

Among the 2881 participants, 478 subjects developed new PAD after 6 years of follow-up. The number of new PAD cases during the course of the study increased across decreasing Ccr quartiles: 108 (15%), 110 (15.3%), 121 (16.9%) and 139 (19.3%) (P = 0.005 for trend; Figure 1). Thus, the incidence of PAD was highest in patients with the worst degree of kidney function at baseline.

The risk of new asymptomatic PAD in each quartile of renal function is depicted in Table 2 in the form of relative risks (RR) for each group. The risk for PAD increased across Ccr quartiles in unadjusted analysis (Table 2). After adjusting for multiple variables including both traditional and non-traditional risk factors, the 4th Ccr quartile

**Fig. 1.** Incident peripheral arterial disease by clearance of creatinine quartiles during the follow-up period.
(<64 mL/min/1.73 m²) retained an independent risk of asymptomatic incident PAD. Similarly, when Ccr was modelled as a linear variable, there was a significant increase in risk for PAD; these associations were unadjusted HR: 1.09 (95% CI 1.03–1.1) and adjusted RR: 1.04 (95% CI 1.01–1.10), per 10 mL/min/1.73 m² decrease in Ccr.

Relationship between baseline kidney function, incident PAD and fatal and non-fatal vascular events

Further analysis was performed to better evaluate the relationship between newly developed PAD and cardiovascular outcomes in patients with CKD and normal or near normal kidney function. During the 6th year of the study period, 163 patients had a fatal and non-fatal vascular event, 124 (5.8%) in the group with a Ccr >60 mL/min/1.73 m² and 39 (8.8%) in the group with a Ccr <60 mL/min/1.73 m² (adjusted RR using Cox regression 1.22; 95% CI [1.05–1.42]; P = 0.01). In addition, the interaction between PAD progression and Ccr was significant (P = 0.04). Therefore, to evaluate the association between baseline kidney function, incident PAD and vascular events, the whole cohort was divided in four groups on the basis of CKD status at baseline and PAD progression. Kaplan–Meier survival curves depicting percent of subjects with cardiovascular events after a 6-year follow-up as a function of creatinine clearance (Ccr) at baseline and incident peripheral arterial disease (log-rank test = 0.0018).

Table 2. Rates and relative risks (95% confidence intervals) of incident peripheral arterial disease events by level of kidney function

<table>
<thead>
<tr>
<th>Model</th>
<th>Quartile 1 (70–89 mL/min/1.73 m²)</th>
<th>Quartile 2 (64–75 mL/min/1.73 m²)</th>
<th>Quartile 3 (58–64 mL/min/1.73 m²)</th>
<th>Quartile 4 (&lt;64 mL/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 720</td>
<td>n = 720</td>
<td>n = 717</td>
<td>n = 720</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.0 (REF)</td>
<td>0.97 (0.91–1.55)</td>
<td>1.33 (1.09–2.11)</td>
<td>1.38 (1.12–2.32)</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>1.0 (REF)</td>
<td>1.06 (0.91–1.64)</td>
<td>1.15 (1.02–1.66)</td>
<td>1.19 (1.07–1.88)</td>
</tr>
<tr>
<td>Fully adjusted</td>
<td>1.0 (REF)</td>
<td>1.01 (0.88–1.19)</td>
<td>1.05 (0.93–1.23)</td>
<td>1.10 (1.01–1.44)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, body mass index, smoking, prevalent ischaemic heart disease, systolic blood pressure, diastolic blood pressure, anti-hypertensive medications, statin administration, aspirin usage, LDL-C, HDL-C triglycerides, HbA1c, hs-C-reactive protein and homocysteine.
Kidney disease and peripheral arterial disease

<table>
<thead>
<tr>
<th>Group</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD−/ABI ≥ 0.9</td>
<td>Referent</td>
</tr>
<tr>
<td>CKD−/ABI &lt; 0.9</td>
<td>1.21 (1.09–2.21)</td>
</tr>
<tr>
<td>CKD+/ABI ≥ 0.9</td>
<td>1.33 (1.13–2.55)</td>
</tr>
<tr>
<td>CKD+/ABI &lt; 0.9</td>
<td>2.05 (1.38–3.99)</td>
</tr>
</tbody>
</table>

CI, confidence interval; HR, hazards ratios.

with CKD at baseline defined as Ccr < 60 mL/min/1.73 m² and incident PAD with lower rates of vascular events in the participants in the other categories, including participants with CKD at baseline but who did not develop PAD during the follow-up period (log-rank test, P = 0.0018). Moreover, in multivariate analysis with the Cox proportional hazard model, participants with baseline CKD and incident PAD had the greatest risk (HR: 2.05; 95% CI 1.38–3.99) of vascular events during the follow-up period (Table 3).

Discussion

This study examined whether there was an association between kidney disease and an incident PAD in a large community-based elderly population. We found that the incidence of asymptomatic PAD increased as the degree of kidney function worsened. Patients with the lowest kidney function level at baseline had the highest rates of incident PAD. Even after adjusting for traditional and non-traditional risk factors for vascular disease, the degree of kidney function proved to be an independent risk factor for development of incident PAD. We also sought to determine if the combination of kidney function level at baseline and incident PAD predicted overall cardiovascular events over the follow-up period. Cardiovascular events were highest in participants with both kidney disease and PAD as compared to either variable examined individually. Thus, the addition of PAD to lower kidney function level appears to provide an increased risk for overall cardiovascular events over time.

There have been very few other studies specifically examining incident PAD in patients with kidney disease. The Atherosclerosis Risk in Communities (ARIC) study demonstrated the increase in PAD with worsening kidney function in a middle-aged cohort [14]. The participants in our study were significantly older and had worse kidney function at baseline compared to those in the ARIC study. Despite the differences in the participant population, the results in both studies were similar in that the risk of incident PAD increased as the degree of kidney function worsened, even after adjusting for other cardiovascular risk factors in both studies. In terms of overall cardiovascular events, prior studies have established an increased risk in cardiovascular outcomes directly related to kidney disease. However, less is known about the association of the combination of kidney disease and incident PAD and risk of vascular events. The Renal Function, Atherothrombosis Extent, and Outcomes in High-Risk Patients Study is the largest study to date examining the risk factors and outcomes of vascular disease in patients with kidney disease [27]. In this international prospective observational study, there was a stepwise increase in the risk of previously established atherothrombosis in any of the three main arterial beds (coronary, cerebral or peripheral) as renal function worsened. However, up to 60% participants in this study did not have an assessment for PAD over the 2-year follow-up. Thus, the combination of kidney disease and PAD has thus far been under-recognized as a risk factor for overall cardiovascular morbidity and mortality.

The increased incidence of PAD in participants with kidney disease highlights the importance of regular screening for this patient population. In addition to traditional risk factors for vascular disease, patients with kidney disease have other contributing factors that are a result of the kidney dysfunction that lead to the high incidence of PAD in this patient group. Such risk factors include abnormal calcium and phosphorous metabolism, inflammation and endothelial dysfunction [9–13]. Furthermore, our study demonstrated the increase in overall vascular outcomes in kidney disease patients that develop new asymptomatic PAD. Thus, the vascular disease appears to not be limited to just the peripheral arterial beds, highlighting the need for vigilance in screening this patient population for cardiac disease that are without symptoms of PAD.

The strengths of this study include the large population size, length of follow-up and the detailed participant clinical data. We were able to adjust for both traditional and non-traditional cardiovascular risk factors, thus strengthening our ability to establish the relationship between kidney disease and PAD. Nevertheless, our study does have limitations: First, we used Ccr to measure renal function, which has its own limitations in its use as a specific marker of true renal function. Second, we do not have details on the aetiology of the underlying renal function. While we are able to adjust for diabetes and hypertension, we are unable to report the underlying cause of renal disease which could have potentially impacted the development of vascular disease. Third, our patient population was older, so caution must be made in terms of applying the results to younger age groups. Similarly, our population was primarily Caucasian making the ability to apply these results to other racial groups limited. Finally, we don’t have results of the degree of proteinuria in our population, which has been shown to be an independent risk factor for CVD [28,29].

In conclusion, our study demonstrated that new cases of PAD increase with lower kidney function levels, independently of traditional risk factors for CVD in elderly patients. Furthermore, the combination of both kidney disease and PAD also increases the risk of overall cardiovascular events. Further studies should examine if more intensive
screening for PAD and therapeutic intervention will reduce cardiovascular morbidity in patients with kidney disease.

Conflict of interest statement. None declared.

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