Impact of subclinical carotid atherosclerosis on incident chronic kidney disease in the elderly

Michel Chonchol¹, Hannes Gnahn² and Dirk Sander³

¹Division of Renal Diseases and Hypertension, University of Colorado Health Sciences Center, Box C-281, Denver, CO 80262, USA, ²INV ADE Study Group, Ebersberg and ³Department of Neurology, Technical University of Munich, Munich, Germany

Abstract

Background. Cardiovascular disease (CVD) is increased in persons with chronic kidney disease (CKD); however, no prospective studies have examined carotid intima-media thickness (CIMT) as a risk factor for CKD.

Methods. A total of 2751 participants who were in the Intervention Project on Cerebrovascular Diseases and Dementia in the community of Ebersberg, Bavaria study and had normal baseline kidney function composed the study cohort. Measures of kidney function were estimated glomerular filtration rate (eGFR) using the Cockcroft–Gault formula in mL/min/1.73 m². The main outcome measure was incident CKD defined as an eGFR < 60 mL/min/1.73 m² at study year 2 among those with an eGFR ≥ 60 mL/min/1.73 m² at baseline. Multivariate Cox regression models were used to assess the association between CIMT and incident CKD.

Results. In multivariate analysis, there was a significant and graded association in eGFR decline, −8 ± 21, −10 ± 22, −11 ± 12 and −15 ± 11 mL/min/1.73 m² for the baseline CIMT quartiles 1 (< 0.66 mm), 2 (0.66–0.77 mm), 3 (0.77–0.88 mm) and 4 (> 0.88 mm), respectively (P for trend: 0.01), during the 2-year follow-up period. Subjects with a baseline CIMT in the fourth quartile developed a significant decrease in eGFR as compared with subjects with a baseline CIMT in the first quartile (P < 0.01). After adjustment for confounding factors, the baseline CIMT remained a predictor for the occurrence of CKD [hazard ratio, 1.17; 95% confidence interval (CI), 1.08–1.30].

Conclusions. Increases in CIMT, as measured non-invasively by ultrasonography, are directly associated with an increased risk of CKD in elderly individuals.

Keywords: atherosclerosis; carotid intima-media thickness; chronic kidney disease

Introduction

Chronic kidney disease (CKD) is becoming an increasingly important health issue worldwide, affecting more than 20 million people in the United States [1,2]. Furthermore, the CKD population is growing rapidly and is expected to exceed 30 million in the United States by 2010 [3]. In fact, progression towards end-stage renal disease (ESRD) exposes CKD patients to an increased risk of development of vascular disease and cardiovascular morbidity and mortality [4,5]. Therefore, the early identification of precursors and risk factors for CKD is essential, as new or established interventions have the potential of delaying progression to renal replacement therapy [6].

Studies that examined the association between CKD and cardiovascular outcomes have shown a high prevalence of kidney disease in persons with established cardiovascular disease (CVD) [7–10]. In addition, prospective studies have shown a positive correlation between increased carotid artery intima-media thickness (CIMT) and the risk for myocardial infarction (MI), stroke and cardiovascular mortality in the general population [11–13] and CVD in ESRD patients [14]. However, there is limited understanding of whether the presence of a subclinical marker of atherosclerosis and CVD, like CIMT [15–17], is an important predictor for progression to CKD.

To examine the prediction power of carotid ultrasonography for the rate of kidney function decline, we examined data from a large, community-based, prospective cohort of elderly subjects. We hypothesized that among persons with normal or near normal kidney function at the initiation of the observation period, the baseline CIMT would be associated with the development of CKD over time.

Subjects and methods

Study population

This investigation is part of the INV ADE (Intervention Project on Cerebrovascular Diseases and Dementia in...
the community of Ebersberg, Bavaria, Germany) study, a prospective and population-based cohort study in the elderly [18]. All inhabitants of the community of Ebersberg, 30 km in the east of Munich, born before 1946, and being members of the health insurance company AOK (‘Allgemeine Ortskrankenkasse’) were identified in the AOK database and were then invited to participate (n = 10 325). In the community of Ebersberg more than 40% of all inhabitants aged > 55 years were AOK members. During the baseline phase (2001–2003), 3905 subjects followed the invitation, of which 3364 participants were included in the present study. The remaining subjects were excluded due to incomplete (n = 365), missing (n = 95) or not analyzable (n = 81) laboratory data for CIMT. The baseline investigation was done by the primary care physicians of the community of Ebersberg (n = 65) and included a standardized questionnaire, a physical examination, evaluation of several risk factors, medical and disease history, a 12-lead electrocardiogram (ECG) and an overnight fasting venous blood sample for analysis in a central laboratory. A duplex ultrasonographic examination of the carotid arteries was done in all subjects according to a standardized protocol by eight experienced investigators after training. All data were entered in a central database after plausibility checks for further evaluation. After the initial baseline investigation the primary care physician evaluated the participants every 3 months. Complete follow-up evaluations were scheduled after 2 years and were available for 3096 participants (91.4%). The local institutional review board approved this investigation. All patients provided informed consent before entering the study. Details of the study design have been recently published in detail [18].

Primary predictor and outcome

Carotid IMT was the main predictor variable for all analyses. Eight experienced investigators performed the duplex ultrasonography using a standardized study protocol. The ultrasound data were stored on video or digital audiotapes, transferred to the neurovascular laboratory of the Department of Neurology and digitalized if necessary. The measurements of mean common carotid artery (CCA) IMT were done as previously described in detail [19] using a computer-supported image analysis system (SigmascanPro 5.0, SPSS). To enhance the reproducibility of carotid measures, standardized interrogation angles were used according to the recommendations described previously [20]. The intra- and interobserver agreements for the measurement of CIMT were 0.93 and 0.83, respectively.

The outcome for the present analysis was incident CKD defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² after 2 years in participants with an eGFR > 60 mL/min/1.73 m² at baseline. We used the Cockroft–Gault formula to measure eGFR [21], which includes measures of age, weight and sex, and was standardized for body surface area using the Dubois formula [22]. For the purpose of this analysis participants with an abnormally high calculated eGFR (>150 mL/min/1.73 m²; n = 17) were excluded.

Baseline covariates

Risk factors determined included the following: body mass index (BMI, kg/m²), smoking status, duration of smoking, alcohol consumption, actual medication, social status, education status, arterial hypertension (treatment with antihypertensive medication or documented blood pressure ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic measured in a standardized fashion) [23], diabetes mellitus (treatment with antidiabetic drugs or overnight fasting serum glucose levels ≥ 7.0 mmol/L), prevalent ischaemic heart disease (documented by previous MI or angina pectoris, by-pass surgery, or ≥ 50% angiographic stenosis of ≥ 1 major coronary artery) and prevalent stroke (neurological deficit that persisted > 24 h, evaluated by a neurologist). MI and stroke were diagnosed according to recent recommendations [24, 25].

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 assessed by a kinetic alkaline picate (Jaffe) method [26]. We used a high-sensitivity assay for the 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 Hi nAuto A1c HA-8140 device (KDK). Levels of total homocysteine were measured by high-performance liquid chromatography with fluorescence detection [27]. The fasting blood samples were collected into EDTA tubes containing 3-deazaneplanocin A (100 mmol/L) [28]. 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, as appropriate. The eGFR differences between subgroups according to the baseline CIMT quartiles were tested with multiple linear regression techniques and the covariate-adjusted mean CIMT values (least-squares means) were reported. Multivariate Cox regression was used to analyse the association between risk factors and the development of incident CKD. All multivariate analyses were adjusted for the same relevant covariates [age, sex, BMI, smoking status, baseline kidney function, prevalent ischaemic heart disease, systolic and diastolic blood pressure, cholesterol, LDL-C, HbA1c, hsCRP, homocysteine and administration of aspirin, statins, angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB)] to ensure giving an
unbiased estimate for the relation between baseline CIMT and incident CKD. Calculations were performed with JMP 5.01 software (SPSS 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 596 (18%) subjects had CKD (eGFR < 60 mL/min/1.73 m$^2$) and 17 subjects (0.5%) had an eGFR > 150 mL/min/1.73 m$^2$ at baseline. From the remaining 2751 subjects, 427 subjects (15.5%) developed an eGFR between 45 and 59 mL/min/1.73 m$^2$, 99 (3.6%) developed an eGFR between 30 and 44 mL/min/1.73 m$^2$ and 22 (0.8%) developed an eGFR < 30 mL/min/1.73 m$^2$ after 2 years of follow-up. The characteristics of participants with and without CKD at close out are shown in Table 1. Compared with those who did not develop CKD, participants with incident CKD were more likely to be older, female, non-smokers, to have a lower BMI, lower triglycerides levels and develop diabetes and hypertension at the end of the follow-up period. Carotid IMT at close out was higher in those with new-onset CKD although their baseline value was comparable to those participants who did not develop CKD. The mean eGFR among participants who progressed to CKD was 78 ± 14 mL/min/1.73 m$^2$ and 50 ± 9 mL/min/1.73 m$^2$ at baseline and at follow-up, respectively.

**Association between CIMT at baseline and incident CKD**

In the multivariate analysis using a Cox regression model, female gender, systolic blood pressure, HbA1c, baseline kidney function and CIMT at the initiation of the study were all significant predictors of developing CKD (Table 2). The use of ACEI or an ARB was associated with a reduced risk of developing CKD, but this relation was only of borderline significance (Table 2). All other tested parameters including baseline age, BMI, smoking status, prevalent ischaemic heart disease, diastolic blood pressure, cholesterol, LDL-C, hsCRP, homocysteine, and aspirin and statin use were not significantly related to the development of CKD. Furthermore, in multivariate analysis there was a significant and graded association between the average rate of eGFR decline during the 2 years of the follow-up period, −8 ± 21, −10 ± 22, −11 ± 12 and −15 ± 11 mL/min/1.73 m$^2$ for baseline CIMT quartiles 1 (<0.66 mm), 2 (0.66–0.77 mm), 3 (0.77–0.88 mm) and 4 (>0.88 mm), respectively (Figure 1; $P$ for trend: 0.01). Subjects with a baseline CIMT in the fourth quartile developed a significant decrease in eGFR after 2 years of follow-up as compared to subjects with a baseline CIMT in the first quartile (Figure 1; $P < 0.01$).

**Discussion**

This investigation demonstrates several important findings that may have implications for therapeutic approaches and future studies. First, in a large population-based sample of elderly persons with baseline normal kidney function, the presence of CVD measured as subclinical carotid atherosclerosis was a predictor for incident CKD. Second, established cardiovascular risk factors including hypertension and HbA1c predicted the development of new kidney disease. Finally, non-traditional risk factors were not found to be important risk factors of new-onset CKD.

This report is the first, to our knowledge, to report that persons with subclinical carotid atherosclerosis are high-risk populations for incident CKD. In this analysis, baseline CIMT was an important predictor of developing CKD after statistical adjustment was made for traditional cardiovascular risk factors including, age, gender, smoking status, systolic and diastolic blood pressure, LDL-C and HbA1C during a 2-year follow-up period. Of note, the strength of the associations between CIMT and the outcome was at least as strong as the associations seen between traditional risk factors and kidney disease progression. For example, an increase of 0.10 mm in CIMT at baseline was associated with a hazard of 1.17 for new development of CKD after adjustment for demographics and clinically relevant cardiovascular risk factors. In contrast, in the same statistical model an increase in systolic blood pressure of 1 mmHg was associated with a hazard of 1.02 and an increase in HbA1C of 1% was associated with a hazard of 1.29. Hence, the strength of the relationship between CIMT and incident CKD when compared with the association between traditional risk factors (i.e. systolic blood pressure, HbA1C) and new onset of CKD, imply that CIMT is by itself an important predictor of kidney disease progression.

Relatively few studies have examined the association between CIMT and kidney function decline. In a recent observational study Szeto et al. [29] reported the renal outcomes of 203 Chinese patients with stage 3–4 CKD. The average CIMT at the baseline of the Asian cohort was comparable to the mean CIMT at the baseline for the patients who developed incident CKD in the INVADE cohort (0.81 ± 0.20 versus 0.79 ± 0.18 mm). In addition, the CIMT quartiles were identical in both populations and the mean rate of kidney function decline was similar for participants in the first, second and third quartile of both cohorts. Of note, a greater decline in kidney function was observed for participants in the fourth quartile in the cohort reported in this analysis. Although in the study by Szeto and colleagues no significant association was noticed between CIMT and renal outcomes, the rate of progression to ESRD during 4 years of follow-up was high when compared to a recently published population-based study [30] evaluating the 9-year risk for ESRD in China (29% versus 24%). The juxtaposition of these results suggests that patients with kidney dysfunction and increased CIMT tend to have a more rapid decline in kidney function when compared to other community-based cohort.

Carotid IMT is increasingly being used as a surrogate marker for atherosclerosis and its ability to predict future clinical cardiovascular endpoints [13]. Recently, Lorenz et al. [31] performed a systematic review and meta-analysis of data examining this association. In this report, the age- and sex-adjusted overall estimates of the risk of MI and stroke were 1.15 (95% CI, 1.12–1.17) and 1.18 (95% CI, 1.16–1.21) per 0.10-mm CIMT difference, respectively. In
Table 1. Characteristics of participants who developed chronic kidney disease (eGFR < 60 mL/min/1.73 m²) during the follow-up period

<table>
<thead>
<tr>
<th></th>
<th>Subjects with eGFR ≥ 60 mL/min/1.73 m² during follow-up (n = 2203)</th>
<th>Subjects that developed eGFR &lt; 60 mL/min/1.73 m² during follow-up (n = 548)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67 ± 5.9</td>
<td>71 ± 7.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>1102 (50%)</td>
<td>110 (20%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.6 ± 4.4</td>
<td>26.4 ± 4.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pack-years of smoking</td>
<td>9.2 ± 18</td>
<td>4.3 ± 12</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prevalent ischaemic heart disease</td>
<td>231 (10.5%)</td>
<td>54 (9.9%)</td>
<td>0.9</td>
</tr>
<tr>
<td>Prevalent stroke</td>
<td>53 (2.4%)</td>
<td>13 (2.4%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Baseline diabetes</td>
<td>416 (18.9%)</td>
<td>101 (18.4%)</td>
<td>0.3</td>
</tr>
<tr>
<td>Follow-up diabetes</td>
<td>483 (21.9%)</td>
<td>156 (28.5%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Baseline Arterial hypertension</td>
<td>1183 (53.7%)</td>
<td>289 (52.7%)</td>
<td>0.44</td>
</tr>
<tr>
<td>Follow-up Arterial hypertension</td>
<td>1348 (61.2%)</td>
<td>405 (74%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>139 ± 18</td>
<td>140 ± 17</td>
<td>0.2</td>
</tr>
<tr>
<td>Diastolic</td>
<td>83 ± 10</td>
<td>82 ± 10</td>
<td>0.1</td>
</tr>
<tr>
<td>Aspirin administration</td>
<td>471 (21.4%)</td>
<td>134 (24.5%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Statin administration</td>
<td>355 (16.1%)</td>
<td>83 (15.1%)</td>
<td>0.6</td>
</tr>
<tr>
<td>ACEI/ARB administration</td>
<td>617 (28%)</td>
<td>162 (29.5%)</td>
<td>0.5</td>
</tr>
<tr>
<td>Blood glucose (mg/dL)</td>
<td>96 ± 33</td>
<td>93 ± 28</td>
<td>0.1</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.8 ± 0.91</td>
<td>5.85 ± 0.84</td>
<td>0.7</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>219 ± 40</td>
<td>221 ± 41</td>
<td>0.5</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>131 ± 40</td>
<td>132 ± 37</td>
<td>0.6</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>150 ± 90</td>
<td>130 ± 69</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>hsCRP (mg/L)</td>
<td>4.0 ± 3.2</td>
<td>3.7 ± 4.1</td>
<td>0.5</td>
</tr>
<tr>
<td>Homocysteine (µmol/L)</td>
<td>6.6 ± 3.7</td>
<td>6.9 ± 3.8</td>
<td>0.1</td>
</tr>
<tr>
<td>Baseline eGFR (mL/min/1.73 m²)</td>
<td>85 ± 16</td>
<td>78 ± 14</td>
<td>0.04</td>
</tr>
<tr>
<td>Follow-up eGFR (mL/min/1.73 m²)</td>
<td>81 ± 17</td>
<td>50 ± 9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline CIMT (mm)</td>
<td>0.78 ± 0.18</td>
<td>0.79 ± 0.18</td>
<td>0.4</td>
</tr>
<tr>
<td>Follow-up CIMT (mm)</td>
<td>0.80 ± 0.19</td>
<td>0.84 ± 0.19</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>IMT progression (mm/year)</td>
<td>0.013 ± 0.027</td>
<td>0.025 ± 0.033</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values expressed as number of participants (percent). Values presented with ± are means ± SD. LDL-C = low-density lipoprotein cholesterol, eGFR = estimated glomerular filtration rate, hsCRP = high-sensitivity C-reactive protein, HbA1c = glycosylated haemoglobin, CIMT = carotid intima-media thickness, ACEI/ARB = angiotensin-converting enzyme inhibitors/angiotensin receptor blockers. P-values are for the difference between groups.

Table 2. Significant predictors of the development of chronic kidney disease (eGFR < 60 mL/min/1.73 m² during follow-up) in subjects without chronic kidney disease at baseline (n = 2751) by multivariate Cox regression analysis

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>1.8 (1.48; 2.35)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic blood pressure (per mmHg increase)</td>
<td>1.02 (1.007; 1.10)</td>
<td>0.04</td>
</tr>
<tr>
<td>HbA1c (per % increase)</td>
<td>1.29 (1.08; 1.39)</td>
<td>0.01</td>
</tr>
<tr>
<td>eGFR at baseline (per 1 mL/min/1.73 m² increase)</td>
<td>0.98 (0.97; 0.997)</td>
<td>0.03</td>
</tr>
<tr>
<td>CIMT at baseline (per 0.10 mm increase)</td>
<td>1.17 (1.08; 1.30)</td>
<td>0.004</td>
</tr>
<tr>
<td>ACEI/ARB administration</td>
<td>0.92 (0.85; 1.0)</td>
<td>0.052</td>
</tr>
</tbody>
</table>

HbA1c = glycosylated haemoglobin, CIMT = carotid intima-media thickness, eGFR = estimated glomerular filtration rate, ACEI/ARB = angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.

Our study, a 0.10-mm CIMT difference increased the hazard of developing kidney disease by 1.17 (95% CI, 1.08–1.30). These findings extend the ability of CIMT in predicting new-onset kidney disease in addition to established cardiovascular endpoints. They further suggest that the pathophysiology that predisposes atherosclerosis to kidney disease becomes operative at early stages. On the basis of the results from this study and previous studies [32–34], one may suggest that atherosclerosis is an important risk factor for incident CKD among individuals with sub-clinical and established CVD.

Several population-based studies have identified hypertension and diabetes to be key risk factors for the development of incident kidney disease [6,35]. Not surprisingly, our data also show systolic hypertension as an important predictor of new-onset kidney disease. In addition, HbA1c, which is an established indicator of average glucose concentrations over a 3-month period and has been suggested as a screening tool for the diagnosis of diabetes [36], was shown to be an important predictor of new-onset kidney disease. These findings confirmed that the most promising future interventions to reduce the risk of kidney disease...
In a recent study from Washington County, Haroun et al. [35] observed an increased risk of kidney disease. The effect of gender on progression of kidney disease in the Modification of Diet in Renal Disease cohort.

Disease progression among the published studies [42,43] are believed to reflect an imbalance in baseline factors, such as age, levels of blood pressure, baseline kidney function and proteinuria. This study has several strengths, including the large, community-based sample, the complete nature of the dataset, the ability to link demographic and clinical factors with patient outcomes, adjustment for multiple traditional and non-traditional cardiovascular risk factors and the use of a clinically important endpoint [incident CKD defined as an eGFR < 60 mL/min/1.73 m²]. Despite the comprehensive nature of the dataset there are some limitations to our study. First, the population consisted of elderly persons with CKD of unknown aetiology; these findings should be applied with caution to younger patients with CKD. Second, the definition of kidney disease was based on a single creatinine measure and it was not possible to confirm that participants who met the criteria did so for a period > 3 months. In addition, inaccurate estimation of kidney function may be responsible for misclassification of some participants in the analyses by stage of kidney function; however, serum creatinine was measured in the same laboratory and using the same technique. Third, we used eGFR rather than more precise measures of kidney function, like iothalamate clearance. Fourth, data regarding other risk factors for kidney disease progression such as microalbuminuria or overt proteinuria were not collected. Fifth, this cohort of participants consisted of predominantly white Caucasians, which limits generalizability. Finally, the follow-up period of 2 years is relatively short.

In conclusion, measurements of CIMT retain predictive power with respect to incident CKD even after traditional and non-traditional risk factors for kidney disease progression have been taken into consideration. These results support the concept that persons with subclinical carotid atherosclerosis should be recognized as a group at high risk for CKD and suggest that a pragmatic approach to decrease the incidence of CKD might include programs targeted at patients with subclinical atherosclerosis. In addition, these findings also raise the issue of whether aggressive treatment of traditional risk factors for subclinical carotid atherosclerosis might, in fact, decrease progression to renal replacement therapy.

Acknowledgement. The Bavarian health insurance company AOK funded this work.

Conflict of interest statement. None declared.

References

22. Dubois D, Bois ED. A formula to estimate the approximate surface area if height and weight are known. *Arch Intern Med* 1916; 17: 863–871

Received for publication: 29.10.07
Accepted in revised form: 10.1.08