Impact of Chronic Kidney Disease on Carotid Atherosclerosis According to Blood Pressure Category

The Suita Study

Tomoyuki Ohara, MD; Yoshihiro Kokubo, MD; Kazunori Toyoda, MD; Makoto Watanabe, MD; Masatoshi Koga, MD; Satoko Nakamura, MD; Kazuyuki Nagatsuka, MD; Kazuo Minematsu, MD; Masanori Nakagawa, MD; Yoshihiro Miyamoto, MD

Background and Purpose—We aimed to clarify the association of chronic kidney disease (CKD) with carotid atherosclerosis and the impact of CKD on carotid atherosclerosis according to blood pressure categories in an urban general population.

Methods—We studied 3,466 Japanese individuals (35–93 years old) in the Suita Study. Carotid atherosclerosis was expressed as the maximum carotid intima-media thickness and the presence of stenosis (>25%). The estimated glomerular filtration rate was calculated using the equations recommended by the Japanese Society of Nephrology. CKD was defined as estimated glomerular filtration rate <60 mL/min per 1.73 m². Blood pressure categories were defined by the European Society of Hypertension and European Society of Cardiology 2007 criteria.

Results—The multivariable-adjusted maximum carotid intima-media thickness and odds ratio for stenosis in subjects with estimated glomerular filtration rate <50 mL/min per 1.73 m² were greater than those in subjects with estimated glomerular filtration rate ≥90 mL/min per 1.73 m². When subjects were stratified according to blood pressure categories, the multivariable-adjusted maximum carotid intima-media thickness was significantly greater in CKD subjects than in non-CKD subjects only in subjects with hypertension. Similarly, the impact of CKD on stenosis was evident only in subjects with hypertension (multivariable-adjusted odds ratios for stenosis [95% confidence interval] were 2.21 [1.53–3.19] in non-CKD/hypertension and 3.16 [2.05–4.88] in CKD/hypertension compared with non-CKD/optimal blood pressure).

Conclusions—In a general population, the association of CKD with carotid atherosclerosis was modest, but CKD was independently associated with carotid atherosclerosis in subjects with hypertension. (Stroke. 2013;44:3537-3539.)

Key Words: carotid artery diseases ■ carotid intima-media thickness ■ hypertension ■ renal insufficiency, chronic

Chronic kidney disease (CKD) has been shown to be an independent risk factor for cardiovascular disease in general populations.1 Recently, we have shown that even slight renal dysfunction, with an estimated glomerular filtration rate (eGFR) of 50 to 59 mL/min per 1.73 m², results in an increased risk of cardiovascular disease in an urban general population.2

One possible explanation for the association of CKD with cardiovascular disease is that CKD-related nontraditional risk factors accelerate atherosclerosis independent of traditional vascular risk factors.3 However, there is controversy as to whether CKD is independently associated with carotid intima-media thickness (IMT).4 This may be because the impact of CKD, especially mild kidney disease, on carotid atherosclerosis is somewhat limited. CKD seems to increase the risk of carotid atherosclerosis when hypertension and impaired glucose metabolism are present.5 We hypothesized that the impact of CKD on carotid atherosclerosis differs according to the presence of concomitant cardiovascular risk factors. Thus, we aimed to clarify the association of CKD with carotid atherosclerosis and the impact of CKD on carotid atherosclerosis according to blood pressure (BP) categories in an urban general population.

Patients and Methods

We sequentially enrolled 3,446 individuals (1,844 women and 1,602 men, 35–93 years old [62±11 years]) who underwent regular health checkups and carotid ultrasonography between April 2002 and March 2004 from the participants in the Suita Study, an epidemiological study of cerebrovascular and cardiovascular diseases. Each index of

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3. This article encompasses the doctoral dissertation of Dr Ohara.
4. The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.113.002957/-/DC1.
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carotid atherosclerosis was defined as follows. Max-IMT was defined as the maximum IMT in the entire scanned area. Stenosis was defined as the presence of a stenotic area ≥25% on a cross-sectional scan. The eGFR was calculated using equations recommended by the Japanese Society of Nephrology. The subjects were categorized into 4 groups (eGFR ≥90, 60–89, 50–59, and <50 mL/min per 1.73 m²) as in our previous study. CKD was defined as an eGFR <60 mL/min per 1.73 m². BP categories (optimal, normal, high-normal BP, and hypertension) were based on the European Society of Hypertension and European Society of Cardiology 2007 criteria. The association of eGFR category with carotid atherosclerosis and the association of CKD with carotid atherosclerosis according to BP categories were examined using analysis of covariance and logistic regression analysis, after adjusting for cardiovascular risk factors as covariates (see Methods in the online-only Data Supplement).

Results

CKD was identified in 16.2% (eGFR=50–59: 10.9%; eGFR<50: 5.3%) of men and in 10.5% (7.4%, 3.1%) of women (see Table I in the online-only Data Supplement). The multivariable-adjusted max-IMT and odds ratio for stenosis in subjects with eGFR<50 were significantly greater than those in subjects with eGFR ≥90; however, the max-IMT and odds ratio in subjects with eGFR=50 to 59 were not significantly different from those in subjects with eGFR ≥90 (Tables 1 and 2). Consequently, the max-IMT and odds ratio for stenosis in the whole CKD sample were not significantly greater than those in the eGFR≥90 group.

When subjects were stratified according to BP categories, the multivariable-adjusted max-IMT in the hypertension category was significantly greater in both sexes. The max-IMT was significantly greater in CKD subjects than in non-CKD subjects only in subjects with hypertension (Figure [A]). The prevalence of stenosis was higher in subjects with high-normal BP and hypertension in all subjects. The impact of CKD on the prevalence of stenosis was more pronounced in subjects with hypertension (multivariable-adjusted odds ratio [95% confidence interval], 2.21 [1.53–3.19] in non-CKD/hypertension and 3.16 [2.05–4.88] in CKD/hypertension; Figure [B]). Similar trends were found in the analysis of stenosis in men.

Discussion

In our study, CKD was independently associated with carotid atherosclerosis in subjects with hypertension, but not in nonhypertensive subjects. This is the first study to show the combined impact of CKD and hypertension on carotid atherosclerosis in an urban general population.

In previous studies in general populations, only one study reported that reduced kidney function was a strong predictor of greater carotid IMT at baseline and progression of carotid atherosclerosis independent of vascular risk factors. Another study found no independent association of eGFR with carotid IMT. In our study, eGFR <50 mL/min per 1.73 m²

<table>
<thead>
<tr>
<th>eGFR, mL/min per 1.73 m²</th>
<th>Odds Ratio/10 mL per min eGFR Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥90</td>
<td>672</td>
</tr>
<tr>
<td>60–89</td>
<td>2320</td>
</tr>
<tr>
<td>50–59</td>
<td>311</td>
</tr>
<tr>
<td>&lt;50</td>
<td>143</td>
</tr>
<tr>
<td>Men</td>
<td></td>
</tr>
<tr>
<td>Age adjusted</td>
<td>47</td>
</tr>
<tr>
<td>Multivariable adjusted</td>
<td>318</td>
</tr>
<tr>
<td>Women</td>
<td>22</td>
</tr>
<tr>
<td>Age adjusted</td>
<td>226</td>
</tr>
<tr>
<td>Multivariable adjusted</td>
<td>226</td>
</tr>
<tr>
<td>Cases of stenosis</td>
<td>1</td>
</tr>
<tr>
<td>Age adjusted</td>
<td>1.09 (0.78–1.53)</td>
</tr>
<tr>
<td>Multivariable adjusted</td>
<td>1.17 (0.83–1.66)</td>
</tr>
<tr>
<td>Men</td>
<td>236</td>
</tr>
<tr>
<td>Cases of stenosis</td>
<td>1106</td>
</tr>
<tr>
<td>Age adjusted</td>
<td>1.37 (0.84–2.23)</td>
</tr>
<tr>
<td>Multivariable adjusted</td>
<td>1.56 (0.94–2.57)</td>
</tr>
<tr>
<td>Women</td>
<td>436</td>
</tr>
<tr>
<td>Cases of stenosis</td>
<td>1214</td>
</tr>
<tr>
<td>Age adjusted</td>
<td>0.85 (0.52–1.37)</td>
</tr>
<tr>
<td>Multivariable adjusted</td>
<td>0.84 (0.51–1.38)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; and eGFR, estimated glomerular filtration rate.
was independently associated with carotid atherosclerosis, whereas CKD was not. The inconsistent results of these studies might be attributable in part to different eligibility criteria, background, or methods for evaluating renal function. An alternative explanation is that the association of CKD with carotid atherosclerosis may be somewhat limited.

In a recent Japanese study, CKD was associated with increased IMT only in subjects with hypertension. Similarly, we showed that CKD was independently associated with carotid atherosclerosis in subjects with hypertension, whereas there was no significant impact of CKD in nonhypertensive subjects. Our results suggest that the impact of CKD on carotid atherosclerosis differs according to the presence of concomitant vascular risk factors. CKD may not directly contribute to early carotid atherosclerosis but may rather accelerate the development of atherosclerosis in the setting of progressive endothelial dysfunction in those with hypertension.

We could not demonstrate a causal relationship between CKD, hypertension, and carotid atherosclerosis because of the cross-sectional design of our study. However, carotid atherosclerosis reflects the cumulative effects of cardiovascular risk factors that are present over many years. In the future, we plan to determine whether the coexistence of CKD and hypertension increases the risk of carotid atherosclerosis in a prospective study.

In conclusion, the association of CKD with carotid atherosclerosis was modest, but CKD was independently associated with carotid atherosclerosis in subjects with hypertension in an urban general population. Our results suggest that the presence of hypertension should be considered for risk stratification of CKD for improved stroke prevention.

Acknowledgments
We thank Drs Masao Shinnomiya and Katsuyuki Kawanishi, the president and vice-president of the Suita Medical Association, respectively, and all members of the Suita Medical Association, the Suita City Health Center, Satsuki-Junyukai, and the Division of Preventive Cardiology.

Figure. Multivariable-adjusted maximum carotid intima-media thickness (max-IMT; A) and odds ratios for stenosis (B) according to blood pressure (BP) category in subjects with and without chronic kidney disease (CKD). *P<0.05; †P=0.053 vs non-CKD/optimal BP; ‡P<0.05 vs non-CKD subjects in the same BP category.

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Disclosures
None.

References
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http://stroke.ahajournals.org/content/suppl/2013/10/01/STROKEAHA.113.002957.DC1

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SUPPLEMENTAL MATERIAL

Impact of chronic kidney disease on carotid atherosclerosis according to blood pressure: The Suita Study

Supplemental Methods

The Suita Study

Suita City is located adjacent to Osaka City, which belongs to the second largest metropolitan area in Japan. The Suita Study, an epidemiological study of cerebrovascular and cardiovascular diseases, is based on a random sampling of 12,200 Japanese urban residents. The participants have been visiting the National Cerebral and Cardiovascular Center every 2 years since 1989 for regular health checkups. Written informed consent was obtained from all participants. This study was approved by the Institutional Review Board of the National Cerebral and Cardiovascular Center.

Evaluation of renal function

Serum creatinine (Cr) was measured by the kinetic Jaffé method. The estimated glomerular filtration rate (eGFR) was calculated from the Cr value and age, using equations recommended by the Japanese Society of Nephrology.\

\[
eGFR \text{ (mL/min/1.73m}^2\text{)} = 194 \times \text{age}^{0.287} \times \text{Cr}^{-1.094} \text{ (for men)}
\]
\[
\text{and } eGFR \text{ (mL/min/1.73m}^2\text{)} = 194 \times \text{age}^{0.287} \times \text{Cr}^{-1.094} \times 0.739 \text{ (for women)}.
\]

Carotid Ultrasound Measurements

Carotid atherosclerosis was evaluated by high-resolution ultrasonography with a 7.5-MHz transducer that produced an axial resolution of 0.1 mm. We measured the carotid arteries from the superior border of the collarbone to the inferior margin of the mandible. Details of the methods used for the carotid ultrasonic examination have been previously published.

Measurement of Blood Pressure
Well-trained physicians measured blood pressure (BP) three times with the subject in a seated position using a mercury column sphygmomanometer, an appropriately sized cuff and a standard protocol. Before the initial BP reading was obtained, participants were seated at rest for at least 5 minutes. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were taken as the average of the second and third measurements, which were separated by more than 1 minute. Subjects were classified into one of four BP categories (optimal, normal, high-normal and hypertension) based on BP values according to the European Society of Hypertension and European Society of Cardiology (ESH-ESC) 2007 criteria: optimal (SBP <120 mmHg and DBP <80 mmHg), normal (SBP=120~129 mmHg and DBP=80~84 mmHg), high-normal BP (SBP=130~139 mmHg and DBP=85~89 mmHg), and hypertensive (SBP ≥140 mmHg and DBP ≥90 mmHg or the use of antihypertensive drugs). If the SBP and DBP readings for a subject were in different categories, the subjects were categorized into the higher of the two BP categories.

Covariates

We performed routine blood tests that included serum total cholesterol, HDL cholesterol and glucose levels. Fasting serum glucose categories were defined as follows: diabetes mellitus (DM, fasting serum glucose ≥7.0 mmol/L (126 mg/dL) or the use of medications for DM), impaired fasting glucose (fasting serum glucose levels from 5.6~6.9 mmol/L (100~125 mg/dL), and normoglycemia (fasting serum glucose levels <5.6 mmol/L (<100 mg/dL). Physicians or nurses administered questionnaires covering personal habits and present illness. Smoking and drinking status were divided into current, former and never. Body mass index (BMI) was calculated as weight (kg) divided by height (m)^2.

Statistical analysis

The association of GFR category with carotid atherosclerosis index was examined using analysis of covariance (ANCOVA) to compare the maximum intima-media thickness among subjects according to GFR category. In addition, logistic regression analysis was to estimate odds ratios (OR) and 95% confidence intervals (CI) for the relationship between stenosis and each GFR category, adjusting for covariates (age, smoking and drinking status, BP category, blood glucose category, total and HDL cholesterol (quartile), and body mass index). To examine the combined impact of CKD and
BP category on carotid atherosclerosis, we analyzed the association between BP category and the carotid atherosclerosis index in subjects with and without CKD, using ANCOVA and logistic regression analysis, adjusting covariates (age, smoking and drinking status, blood glucose category, total and HDL cholesterol and body mass index). A P value <0.05 was considered significant for all comparisons. All analyses were performed with SAS statistical software (version 8.2; SAS Institute, Cary, NC, USA).
**Supplemental Table I. Characteristics of study subjects according to eGFR category**

<table>
<thead>
<tr>
<th></th>
<th>GFR in men, mL/min/1.73m² (n = 1602)</th>
<th>GFR in women, mL/min/1.73m² (n = 1844)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤90</td>
<td>60-89</td>
</tr>
<tr>
<td>Patients, n</td>
<td>236</td>
<td>1106</td>
</tr>
<tr>
<td>Age, y</td>
<td>57±11</td>
<td>67±11</td>
</tr>
<tr>
<td>BP category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optimal BP, %</td>
<td>31</td>
<td>20</td>
</tr>
<tr>
<td>Normal BP, %</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>High normal BP, %</td>
<td>13</td>
<td>17</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>38</td>
<td>44</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>199±33</td>
<td>199±31</td>
</tr>
<tr>
<td></td>
<td>59±16</td>
<td>55±14</td>
</tr>
<tr>
<td>--------------------------</td>
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<tr>
<td>HDL cholesterol, mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23±3</td>
<td>23±3</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>43</td>
<td>29</td>
</tr>
<tr>
<td>Current drinking, %</td>
<td>74</td>
<td>68</td>
</tr>
</tbody>
</table>

Values are the means±standard deviation or percent.

GFR, glomerular filtration rate; BP, blood pressure; HDL, high-density lipoprotein
Supplemental References


