Correlation between Peripheral Arterial Disease and Stage of Chronic Kidney Disease

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Background: Atherosclerotic disease is the most common disease in clinical practice. Risk factors for the disease include diabetes, hypertension, dyslipidemia, smoking and chronic kidney disease (CKD). However, few studies have reported the correlation between peripheral arterial disease (PAD) and stages of CKD. Ankle brachial index (ABI) is a non-invasive method for detecting PAD with high sensitivity and specificity.

Objective: We studied the prevalence of asymptomatic PAD in patients with each stage of CKD using ABI measurement.

Material and Method: We conducted a study of patients with CKD classified by the Kidney Disease Outcomes Quality Initiative classification (K/DOQI classification) who attended at outpatient clinics. The patients with symptomatic PAD will be excluded. The participants will be sent to ABI measurement for the diagnosis of PAD, defined as ABI less than 0.9.

Results: The total number of patients who had been enrolled in the study was 201; Male 55%. Mean age was 63.16 ± 11.3 years. 22.4% of the patients have ABI less than 0.9 which was associated with older age, being female, and having lower diastolic blood pressure (p = 0.002, < 0.001, < 0.0001, respectively). Diabetes and coronary artery disease were higher in patients with abnormal ABI but with no statistical significance. No difference in other risk factors, for example, hypertension, dyslipidemia and smoking, was detected. Abnormal ABI was frequently seen in the patients with more advanced CKD and mean ABI was lower in patients with more advanced CKD stage. The mean ABI of stage 4 and 5 CKD patients was lower than that of stage 1 and 2 (p < 0.05).

Conclusion: The prevalence of asymptomatic PAD increased with more advanced stage of CKD.

Keywords: Peripheral arterial disease, Chronic kidney disease, Ankle-brachial index

Peripheral arterial disease (PAD) is common in clinical practice. From the previous study in Siriraj hospital, the prevalence of PAD was 1.02 in 1,000 patients(1). Most of PAD patients were found too late and already symptomatic. Risk factors of PAD were old age, diabetes, hypertension and smoking, etc. The high relative risk factors were diabetes and smoking(2). PAD is a form of atherosclerosis as is coronary artery disease and cerebrovascular disease.

In clinical practice, the patients have many comorbidities such as diabetes, hypertension, dyslipidemia and also chronic kidney disease (CKD), which made for poor quality of life and increased morbidity and mortality(3,4).

Although chronic kidney disease is not a major risk factor for PAD, few studies(5-8) had shown the relationships not only in asymptomatic patients but also symptomatic patients.

Diagnosis of PAD was consisted of history, physical examination and investigations. To date, ankle brachial index (ABI) remains a non-invasive and inexpensive diagnostic test. An ABI < 0.9 is 95% sensitive and 100% specific for angiographically documented PAD for arterial stenosis > 50% in the lower extremities(9).

Cardiovascular Health Study(10) had reported higher prevalence of abnormal ABI in renal insufficiency when compared with normal renal function (12%, 7%). Other previous studies(11,12) also reported abnormal ABI in patients with CKD stage 3-5 (defined by Kidney Disease Outcomes Quality Initiative classification (K/DOQI classification) which were 24% and 32%, respectively.
In this study we investigated correlation between asymptomatic PAD in each stage of CKD. We hypothesized that advanced stage of CKD would have more asymptomatic PAD than earlier stage. The findings might lead to appropriate screening and earlier treatment.

Material and Method

The study was done between October 2009 and February 2010 in adult patients who visited at outpatient department, Siriraj Hospital. We enrolled 201 patients with all stages of chronic kidney disease as defined by Kidney Disease Outcomes Quality Initiative classification (K/DOQI classification). They were not previously diagnosed with PAD; the disease that caused chronic ulcer at lower extremities or intermittent claudication. Although in early stage of CKD patients might have normal creatinine, but would have structural kidney damage confirmed by kidney biopsy. The patient who were on hemodialysis or peritoneal dialysis, were handicapped and those who refused the study would be excluded from the study. Blood chemistry in past 3 months, medical record, body weight and height were reviewed and then the stage of chronic kidney disease was calculated by using Cockroft-Gault formula equation. Then each stage of CKD patients was sent to measure ABI.

ABI was calculated using a portable pulse detector (VaSera VS-1000, Fukuda Denshi, Tokyo, Japan). Systolic blood pressure (SBP) measurement was taken in both arms and legs after 10 minutes at rest in supine position. The ABI was calculated for each leg on the basis of the SBP of the arm where this was highest and according to the formula;

\[
\text{ABI} = \frac{\text{SBP in posterior tibial artery or dorsalis pedis artery/brachial SBP}}
\]

ABI < 0.9 in one of the legs was considered as abnormal ABI, and ABI ≥ 0.9 considered as normal ABI. The patients who had abnormal ABI was diagnosed asymptomatic PAD.

Primary endpoint was the correlation between asymptomatic PAD and each stage of CKD patients, and secondary endpoint was prevalence of asymptomatic PAD in CKD patients.

Statistical analysis

The study design was cross-sectional observational descriptive study. Quantitative data was expressed as mean ± SD and qualitative data was expressed as percent. All statistical analysis was performed using a computerized statistical package, SPSS for Windows (Inc, an IBM, Chicago, Illinois, USA). Chi-square test was used to assess the differences of proportion of categorical variables between abnormal ABI and normal ABI groups, and student t-test was used to analyze differences in continuous variables between abnormal ABI and normal ABI. ANOVA (1-way) was used to analyze differences in ABI between CKD stages.

Results

Two hundred and one patients were enrolled and forty-five patients (22.4%) had an abnormal ABI. Baseline characteristics and comparison of patients with normal and abnormal ABI are shown in Table 1.

Most patients were male of old age and nonsmokers. Hypertension, dyslipidemia and coronary artery disease were common co-morbid diseases. Medications were aspirin, beta-blocker and statin. Baseline systolic blood pressure and blood chemistry were similar in both groups.

Patients with an ABI < 0.9 were mainly of older age, female exhibited worse renal function than males and had lower diastolic blood pressure.

We found incremental correlation between prevalence of abnormal ABI and stage of chronic kidney disease (Fig. 1); 9.5% in Stage 1; 14.3% in stage 2, 21% in stage 3; 36-37% in stage 4-5.

By comparing each stage with stage 1 (Table 2), the odd ratio for stage 2 was 1.6, for stage 3 was 2.5 and those for stage 4, 5 were around 5 which were of statistical significance (95% CI 1.1-27.4 and 1.1-30.4, respectively).

Fig. 2 shows mean ABI in each stage of CKD; mean ABI of stages 1-3 were about 1.0, whereas  mean ABI of stages 4 and 5 were 0.98 and 0.97, respectively (p < 0.05).

Discussion

Our study confirmed correlation between asymptomatic PAD, defined by abnormal ABI (ABI < 0.9), and CKD. The patient with advanced stages of CKD had higher abnormal ABI rate than those in earlier stage. Moreover, mean ABI was lower in patients with the advanced stages. This is the first study to demonstrate an incremental association between PAD and CKD stages. However, this study did not include patients who were on hemodialysis because they had arteriovenous fistula (AVF), which might be damaged or thrombosed when ABI measurement was performed. This study found that an ABI < 0.9 were associated with older age, female gender, worse renal function and
Table 1. Baseline characteristic of patients and comparison of patients with normal and abnormal ABI

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 201)</th>
<th>Abnormal ABI (n = 45)</th>
<th>Normal ABI (n = 156)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>201</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>65.2 ± 11.3</td>
<td>70 ± 10.7</td>
<td>63 ± 11.0</td>
<td>0.002</td>
</tr>
<tr>
<td>Female gender</td>
<td>90 (44.78%)</td>
<td>32 (71%)</td>
<td>58 (37.2%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Diabetes</td>
<td>78 (38.8%)</td>
<td>21 (46.7%)</td>
<td>57 (36.5%)</td>
<td>0.29</td>
</tr>
<tr>
<td>- Hypertension</td>
<td>158 (78.6%)</td>
<td>35 (77.8%)</td>
<td>123 (78.8%)</td>
<td>1.0</td>
</tr>
<tr>
<td>- Dyslipidemia</td>
<td>163 (81.1%)</td>
<td>38 (84.8%)</td>
<td>125 (80.1%)</td>
<td>0.66</td>
</tr>
<tr>
<td>- Coronary artery disease</td>
<td>125 (62.2%)</td>
<td>30 (66.7%)</td>
<td>95 (60.9%)</td>
<td>0.60</td>
</tr>
<tr>
<td>- Immunocompromise</td>
<td>2 (1%)</td>
<td>0 (0%)</td>
<td>2 (1.3%)</td>
<td>1.0</td>
</tr>
<tr>
<td>History of smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Current smoke</td>
<td>10 (5%)</td>
<td>1 (2.2%)</td>
<td>9 (5.8%)</td>
<td>0.49</td>
</tr>
<tr>
<td>- Quit smoke</td>
<td>23 (11.4%)</td>
<td>4 (8.9%)</td>
<td>19 (12.2%)</td>
<td></td>
</tr>
<tr>
<td>- Non-smoke</td>
<td>168 (83.6%)</td>
<td>40 (88.9%)</td>
<td>128 (82.1%)</td>
<td></td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Aspirin</td>
<td>169 (84.1%)</td>
<td>39 (86.7%)</td>
<td>130 (83.3%)</td>
<td>0.76</td>
</tr>
<tr>
<td>- Plavix</td>
<td>115 (57.2%)</td>
<td>21 (46.7%)</td>
<td>94 (60.3%)</td>
<td>0.15</td>
</tr>
<tr>
<td>- Beta blocker</td>
<td>138 (68.7%)</td>
<td>34 (75.6%)</td>
<td>104 (66.7%)</td>
<td>0.34</td>
</tr>
<tr>
<td>- ACE-I</td>
<td>59 (29.6%)</td>
<td>11 (25%)</td>
<td>48 (31%)</td>
<td>0.56</td>
</tr>
<tr>
<td>- ARB</td>
<td>53 (26.4%)</td>
<td>14 (31.1%)</td>
<td>39 (25%)</td>
<td>0.53</td>
</tr>
<tr>
<td>- Calcium blocker</td>
<td>61 (30.3%)</td>
<td>13 (28.9%)</td>
<td>48 (30.8%)</td>
<td>0.95</td>
</tr>
<tr>
<td>- Diuretics</td>
<td>53 (26.4%)</td>
<td>16 (35.6%)</td>
<td>37 (23.7%)</td>
<td>0.16</td>
</tr>
<tr>
<td>- Statins</td>
<td>162 (80.6%)</td>
<td>35 (77.8%)</td>
<td>127 (81.4%)</td>
<td>0.74</td>
</tr>
<tr>
<td>- Nitrates</td>
<td>76 (37.8%)</td>
<td>15 (33.3%)</td>
<td>61 (39.1%)</td>
<td>0.60</td>
</tr>
<tr>
<td>- Fibrates</td>
<td>3 (1.5%)</td>
<td>0 (0%)</td>
<td>3 (1.9%)</td>
<td>0.81</td>
</tr>
<tr>
<td>- Vasodilator</td>
<td>22 (10.9%)</td>
<td>7 (15.6%)</td>
<td>15 (9.6%)</td>
<td>0.39</td>
</tr>
<tr>
<td>Body mass index (BMI)</td>
<td>24.9 ± 4.8</td>
<td>24.6 ± 5.3</td>
<td>25.0 ± 4.7</td>
<td>0.61</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>155.3 ± 28.9</td>
<td>155.8 ± 31.3</td>
<td>155.2 ± 28.3</td>
<td>0.91</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>78.6 ± 13.1</td>
<td>72.4 ± 13.9</td>
<td>80.4 ± 12.3</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>51.8 ± 29.9</td>
<td>40.8 ± 29.7</td>
<td>55 ± 29.2</td>
<td>0.01</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.99 ± 2.4</td>
<td>2.4 ± 2.8</td>
<td>1.9 ± 2.2</td>
<td>0.17</td>
</tr>
<tr>
<td>Fasting blood sugar (mg/dl)</td>
<td>114.9 ± 40.4</td>
<td>119 ± 36.7</td>
<td>113.3 ± 41.6</td>
<td>0.40</td>
</tr>
<tr>
<td>HbA1c</td>
<td>7.2 ± 1.3</td>
<td>6.8 ± 0.9</td>
<td>7.4 ± 1.5</td>
<td>0.08</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>167.1 ± 40.8</td>
<td>167.3 ± 37.9</td>
<td>167.1 ± 41.8</td>
<td>0.98</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>134.8 ± 73.6</td>
<td>121.5 ± 53.9</td>
<td>138.9 ± 78.4</td>
<td>0.24</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>43.6 ± 12.5</td>
<td>45.5 ± 14.4</td>
<td>42.9 ± 11.9</td>
<td>0.31</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>98.2 ± 35.1</td>
<td>100.2 ± 34.4</td>
<td>97.5 ± 35.5</td>
<td>0.68</td>
</tr>
<tr>
<td>Calcium</td>
<td>8.8 ± 0.7</td>
<td>8.4 ± 0.6</td>
<td>9.2 ± 0.5</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Table 2. Correlation between abnormal ABI and CKD (defined by ABI <0.9) with odd ratio compared with stage 1

<table>
<thead>
<tr>
<th>Stage</th>
<th>Odd ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1.6</td>
<td>0.3-8.1</td>
</tr>
<tr>
<td>3</td>
<td>2.5</td>
<td>0.5-12.1</td>
</tr>
<tr>
<td>4</td>
<td>5.4</td>
<td>1.1-27.4</td>
</tr>
<tr>
<td>5</td>
<td>5.7</td>
<td>1.1-30.4</td>
</tr>
</tbody>
</table>

Compared with previous studies, our prevalence of asymptomatic PAD in patient with renal insufficiency (Creatinine clearance < 60 mL/min-1) was somewhat similar to the study by O’Hare et al in the National Health and Nutrition Examination Survey (NHANES) 1999-2000 (11) (28% and 24%, respectively).
the total patients in the study were not enough to demonstrate epidemiologic.

Conclusion
The prevalence of asymptomatic PAD increased with more advanced stage of CKD which was defined by K/DOQI classification.

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Potential conflicts of interest
None.

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