The Prevalence and Correlated Factors of Peripheral Artery Disease in Patients with Chronic Kidney Disease

Ching-Ping Yang¹, Chin-Yen Tsai², and Shu-Chuan Jennifer Yeh³

¹Division of Nephrology, Kaohsiung Municipal Min-Sheng Hospital;
²Department of Pediatrics, Yuan’s General Hospital;
³Department of Business Management, Institute of Health Care Management, National Sun Yat-Sen University, Kaohsiung, Taiwan

Abstract

Patients with chronic kidney disease (CKD) are at increased risk for atherosclerosis and peripheral artery disease (PAD). We studied the possible related risk factors and hypertension treatment in CKD patients with PAD. One hundred and twenty-four patients with stages 3 to 5 of CKD, as described by the Kidney Outcome Quality Initiatives (K/DOQI) classification, were included in this study. Neither the patients on dialysis nor with PAD were included. The ankle-brachial index (ABI) was calculated using the Fukuda Vascular Screening system VaSera VS-1000™. Patients were diagnosed with PAD if the ABI for one of the legs was <0.9. Patient characteristics and their laboratory data were collected. There were 22 (17.7 %) participants with PAD. Higher systolic blood pressure, higher diastolic blood pressure, and increased pulse pressure showed a strong association with PAD. On further analysis, significantly fewer patients were treated with calcium channel blocker in hypertensive CKD patients with PAD ($\chi^2$ =7.055, p=0.008). The multiple logistic regression analysis in hypertensive patients demonstrated the risk factors for PAD was pulse pressure, and calcium channel blocker treatment negatively correlate with ABI<0.9 in CKD patients (odds ratio=0.232, 95% CI = 0.07-0.73, p=0.013). There was a high prevalent rate of PAD in CKD patients, especially those with hypertension. ABIs may be routinely used for early diagnosis and therapeutic management. (J Intern Med Taiwan 2010; 21: 48-55)

Key Words: Ankle brachial index; Chronic kidney disease; Calcium channel blocker; Hypertension; Peripheral artery disease

Introduction

Patients with chronic kidney disease (CKD) are at increased risk for atherosclerosis and cardiovascular diseases, which include coronary artery disease, congestive heart failure, and peripheral artery disease (PAD)¹². PAD is traditionally defined by an ankle-brachial index (ABI) of <0.9. However, CKD patients with PAD have received far less attention than coronary artery disease (CAD), but more studies have examined risk factors for CKD patients with PAD recently¹⁴. In the general population, many of the traditional coronary risk factors are also risk factors for PAD, such as age, male gender, diabetes, hypertension, smoking and...
hyperlipidemia. Other novel risk factors, such as C-reactive protein, lipoprotein, and tissue plasmino

gen activator have also been associated with PAD. CKD patients often present with traditional
risk factors such as diabetes, hypertension, or hyperlipidemia, as well as non-traditional risk
factors, such as malnutrition, inflammation, and oxidative stress. PAD is increasingly recognized
as an important contributor to adverse outcomes in patients who have CKD. However, over one-half
of those with PAD in the general population remain asymptomatic and lack clinical attention and
documentation.

To diagnose asymptomatic PAD, ABI is used as a noninvasive diagnostic test that is easily and
efficiently performed. It has been shown to be a strong predictor of cardiovascular disease and
mortality. ABI < 0.9 has 95% sensitivity and 100% specificity for PAD compared with invasive
angiography.

Screening for early diagnosis and treatment of PAD in CKD patients is very crucial for preventing
arterial occlusion progression, distal ischemia, and cardiovascular morbidity. Therefore, the purposes
of this study were to examine the prevalence of PAD in non-dialyzed patients with stage 3-5 CKD,
as described by the K/DOQI, using ABIs and the relative risk factors related to PAD in CKD patients.

Materials and Methods

This study was performed between May and September 2008. We included 124 consecutive
adult non-dialysis patients seen in our nephrology outpatient clinic with stage 3 to 5 CKD (K/DOQI
classification) who were not previously diagnosed with PAD.

Measurements

All patients had estimated glomerular filtration rate (eGFR) < 60ml/min/1.73m², as calculated by
the Modification of Diet in Renal Disease (MDRD) equation. Medical records were reviewed for his-
tory of hypertension, diabetes, smoking, pre-existing cardiovascular disease, and the use of
anti-hypertension drugs or lipid-lowering agents (statins). Hypertension was diagnosed according
to history or if the blood pressure was >140/90 mmHg, which was measured with a standard cuff
mercury sphygmomanometer from the right or left arm with patients in a sitting position. For patients
without a history of hypertension, the average of two measurements at two or more visits after an
initial screen were recorded at least five minutes apart in our clinical office.

Diabetes was diagnosed according to the past medical history, if the patient received pha-
rmacologic treatment, or if the fasting plasma glucose (FPG) was >126 mg/dL or the 2 hr PG was
>200 mg/dL. Pre-existing coronary heart disease (CHD) and cerebro-vascular disease (CVD) were
diagnosed according to documented history of coronary artery disease or stroke. Body mass index
(BMI) was calculated using a formula of body weight (kg) / body height (m)². Additionally, fast-
ing blood glucose, HbA1c, total cholesterol, triglyceride (TG), high density lipoprotein cho-
lesterol (HDL), low density lipoprotein cholesterol (LDL), calcium (Ca), phosphorus (P), albumin,
uric acid, and urine protein values were measured within a 6 month period prior to the commencement of
the study. Individuals were classified as having proteinuria (urine dipstick: 1+, 2+, 3+, 4+) and non-
proteinuria (urine dipstick: negative or trace).

The ABI was calculated using the Fukuda Vascular Screening system VaSera VS-1000™
(Fukuda Denshi Co. Ltd., Tokyo, Japan). Subjects rested for 5 min, then the blood pressures at both
upper arms and ankles were measured to obtain the ABI using the VS-1000™. An ABI between 0.9 and
1.3 in both legs was considered normal. Patients were diagnosed with PAD if the ABI for one of the
Table 1. Characteristics of the study population (n=124)

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>males 87(70.2%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>70.75±9.9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.38±3.96</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>153.01±23.15</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>88.10±12.4</td>
</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
<td>64.91±15.35</td>
</tr>
<tr>
<td>Hypertension</td>
<td>104(83.87%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>55(44.4%)</td>
</tr>
<tr>
<td>Smoker</td>
<td>31(25%)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>60(48.4%)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>6(4.8%)</td>
</tr>
<tr>
<td>Serum albumin(g/dL)</td>
<td>3.9±0.45</td>
</tr>
<tr>
<td>Proteinuria *</td>
<td>74(60.7%)</td>
</tr>
<tr>
<td>PAD</td>
<td>22(17.7%)</td>
</tr>
</tbody>
</table>

Notes: 1.BMI = Body Mass Index; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; PAD = Peripheral artery disease. 2. *two patients urine protein data neglected. 3.Data are presented as mean ± SD.

legs was <0.9. ABI >1.3 suggested a non-compressible calcified vessel and might require other test to diagnose PAD.

Statistical analysis

All statistical analyses were performed using SPSS (SPSS, Version 12.0; SPSS Inc., Chicago, IL, USA). The results are presented as mean ± standard deviation. Chi-square tests were used to examine the association between qualitative variables, and student t-tests were used to analyze mean differences between PAD and normal patients. In addition, logistic regression analysis was used to calculate the odds ratios (OR) of independent risk factors of PAD.

Results

One hundred and twenty-four patients were enrolled in this study and received ABI measurements. The demography and baseline characteristics of the study populations can be seen in Table 1. There were 22 (17.7%) participants with PAD and 7 (31.8%) patients demonstrated clinical symptoms of PAD by history taking. There was no patient with ABI >1.3. There were 31.8% of PAD patients used statins, while 18.6% of non-PAD patients used statins.

Table 2 compares risk factors of CKD patients with and without PAD (Table 2). We found that PAD patients had a higher percentage of hypertension (100% vs. 80.4%, p=0.02), which included higher systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure. We observed no differences between patients with and without PAD in mean age, gender, smoking history, diabetes mellitus, and proteinuria. In addition, no significant differences were found in serum creatinine, eGFR, albumin, cholesterol, triglyceride level, and statin usage between the two groups.

Table 3 compares drug use in our hypertensive patients with and without PAD. We found significantly fewer hypertensive patients treated with calcium channel blockers (χ² =7.055, p=0.008). The multiple logistic regression analysis in hypertensive patients after adjustment for age, diabetes, smoking, and male gender (Table 4) demonstrated that pulse pressure was a risk factor for PAD with an odds ratio (OR) of 1.064 (95% CI = 1.024-1.106, p=0.002). Calcium channel blocker treatment may negatively correlate with ABI<0.9 (OR = 0.232; 95% CI = 0.07-0.73, p = 0.013).

Discussion

Like CHD and CVD, PAD is a major arterial disease caused by atherosclerosis. Subclinical PAD is a chronic systemic disease caused by occlusion and reduced blood flow in the lower extremities without obvious signs and symptoms, so the disease may be easily overlooked. However, as PAD progresses, claudication, ischemic changes, and necrosis of the feet can occur. PAD is now known to be a major risk factor of CHD and CVD. According to the Adult treatment panel III of National Cholesterol Education Program, PAD should be regarded as being equivalent to DM as a CHD risk factor.
Table 2. Comparison of risk factors in patients with PAD and non-PAD

<table>
<thead>
<tr>
<th>Variables</th>
<th>PAD (N=22)</th>
<th>Non-PAD (102)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>age (years)</td>
<td>72.5±11</td>
<td>70.37±9.66</td>
<td>0.36</td>
</tr>
<tr>
<td>Male gender*</td>
<td>16 (72.7%)</td>
<td>71 (69.6%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>22 (100%)</td>
<td>82 (80.4%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Diabetes mellitus*</td>
<td>12 (54.5%)</td>
<td>43 (42.2%)</td>
<td>0.28</td>
</tr>
<tr>
<td>CHD*</td>
<td>11 (50%)</td>
<td>49 (48%)</td>
<td>0.87</td>
</tr>
<tr>
<td>CVD*</td>
<td>2 (9.1%)</td>
<td>4 (3.9%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Smoking history*</td>
<td>7 (31.8%)</td>
<td>24 (23.5%)</td>
<td>0.42</td>
</tr>
<tr>
<td>SBP(mmHg)</td>
<td>170.64±33.17</td>
<td>149.21±18.48</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP(mmHg)</td>
<td>94.50±18.17</td>
<td>86.72±10.38</td>
<td>0.007</td>
</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
<td>76.14±21.18</td>
<td>62.49±12.67</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI(kg/m²)</td>
<td>24.94±4.09</td>
<td>25.48±3.94</td>
<td>0.56</td>
</tr>
<tr>
<td>Creatinine(mg/dL)</td>
<td>3.06±1.53</td>
<td>2.89±1.95</td>
<td>0.70</td>
</tr>
<tr>
<td>eGFR (ml/min)¹</td>
<td>25.47±12.04</td>
<td>27.97±14.50</td>
<td>0.45</td>
</tr>
<tr>
<td>Cholesterol(mg/dL)</td>
<td>194.68±60.78</td>
<td>181.07±45.78</td>
<td>0.24</td>
</tr>
<tr>
<td>Triglyceride(mg/dL)</td>
<td>151.09±92.27</td>
<td>170.74±107.23</td>
<td>0.43</td>
</tr>
<tr>
<td>HDL(mg/dL)</td>
<td>48.90±12.68</td>
<td>46.27±11.12</td>
<td>0.33</td>
</tr>
<tr>
<td>LDL(mg/dL)</td>
<td>110.82±40.69</td>
<td>102.43±33.41</td>
<td>0.31</td>
</tr>
<tr>
<td>Using statins*</td>
<td>7 (31.8%)</td>
<td>19 (18.6%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Albumin(g/dL)</td>
<td>3.81±0.45</td>
<td>3.93±0.45</td>
<td>0.25</td>
</tr>
<tr>
<td>Calcium(mg/dL)</td>
<td>9.30±0.57</td>
<td>9.30±0.77</td>
<td>0.97</td>
</tr>
<tr>
<td>Phosphate(mg/dL)</td>
<td>3.74±0.95</td>
<td>3.67±0.90</td>
<td>0.72</td>
</tr>
<tr>
<td>Uric acid(mg/dL)</td>
<td>6.93±2.36</td>
<td>6.67±1.89</td>
<td>0.58</td>
</tr>
<tr>
<td>Proteinuria”²</td>
<td>16 (72.7%)</td>
<td>58 (58%)</td>
<td>0.20</td>
</tr>
<tr>
<td>HbA1c</td>
<td>6.65±2.50</td>
<td>6.45±1.58</td>
<td>0.65</td>
</tr>
<tr>
<td>Sugar AC (mg/dL)</td>
<td>112.71±35.66</td>
<td>114.10±38.07</td>
<td>0.88</td>
</tr>
</tbody>
</table>

Notes: 1. CHD = coronary heart disease; CVD = cerebral vascular disease; eGFR = estimated glomerular filtration rate; HDL = high density lipoprotein cholesterol; LDL = low density lipoprotein cholesterol; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; HbA1C = Glycated Hemoglobin.
2. *Chi-square test used.
3. **two patients urine protein data neglected.
4. Data are presented as mean±SD.

PAD affects approximately 5% of adults in the United States who are 40 years and older²⁰. Hypertensive patients with stage 3-5 CKD have a higher prevalence rate (21.1%) of PAD, compared to hypertensive patients without renal insufficiency (prevalence 6.9%)²¹. The results from the NHANES 1999-2000 survey also showed a remarkably high prevalence (24%) of PAD among patients with renal insufficiency³. Our data also revealed a high prevalence rate (17.7%) in non-dialyzed patients with stage 3-5 CKD and a high prevalence rate (21.2%) in hypertensive patients in our study population compared with general United States population²⁰.

Subclinical PAD has received far less attention than CHD given the lack of clinical symptoms and the consequences leading to adverse outcomes. Routine ABI measurement in CKD patients would greatly enhance efforts in detecting subclinical PAD³. ABI is a standard non-invasive diagnostic test for PAD. The technique is well validated, and values are predictive of cardiovascular morbidity and mortality²².

The risk factors for PAD in the general population included increasing age, male gender, hypertension, diabetes mellitus, smoking, and hypercholesterolemia⁷,²¹. In our study, we did not see a significant difference between the PAD and non-PAD group with regards to the risk factors of increasing age, male gender, diabetes mellitus,
smoking, decreasing GFR and hypercholesterolemia. We also found that our prevalence rate (17.7%) of PAD in CKD patients is lower than that described in the NHANES study (24%) and in a Spanish population of patients with CKD (32%). However, there were higher percentages of men, diabetics, and smokers and a lower percentage of statins users included in our study compared with the other two studies. These findings may be due to race difference between these studies. When the prevalent rate was stratified to CKD stage, we also found that stage 5 CKD had a high PAD prevalent rate (20%), as well as stage 4 (22%) and stage 3 (14%). Therefore, if more CKD patients were included in our study, we may have seen a greater difference between the risk factors.

Hypertension contributes to the pathogenesis of atherosclerosis, which is the basic pathological process underlying PAD. Untreated hypertension and treated but uncontrolled hypertension are important risk factors for PAD, with a near doubling of the OR for PAD after adjustment for other risk factors. After logistic regression, systolic blood pressure confirmed an OR for PAD of 1.3 per 10 mmHg systolic pressure. Of the patients included in our study, 83.9% of CKD patients have hypertension. All PAD patients were hypertensive. After univariate analysis of risk factors with PAD, we found statistically significant relationships between systolic blood pressure and diastolic blood pressure in PAD patients with CKD, which supports the correlation between hypertension and PAD. Pulse pressure after logistic regression analysis resulted in an OR for PAD of 1.64 (95% CI = 1.024-1.106) per 1 mmHg pulse pressure. Therefore, it is important to consider ABI screening in hypertensive CKD patients.

In patients with PAD, hypertension is a major associated cardiovascular risk factor in up to 55% of these patients. However, PAD is often under diagnosed and hypertension in PAD is more frequently poorly managed.

In the Heart Outcome Protection Evaluation Study (HOPE) trial, a randomized, placebo-controlled trial demonstrated a reduction in cardiovascular events in patients who had PAD based on ABI<0.9 and were treated with ramipril. The cardiovascular event reduced from 17.7% (placebo) to 14.1% (ramipril). However, angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) may decreased eGFR and lead to a rise of creatinine. Therefore, ACEI and ARB should be used with caution in CKD patients.

The Valsartan Antihypertensive Long-term

### Table 3. Comparison of drug used in hypertensive CKD patients with PAD and non-PAD

<table>
<thead>
<tr>
<th>Anti-hypertension drug</th>
<th>PAD (n=22)</th>
<th>Non-PAD(n=82)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium channel blocker</td>
<td>7(31.8%)</td>
<td>52(63.4%)</td>
<td>0.008</td>
</tr>
<tr>
<td>ACEI</td>
<td>5(22.7%)</td>
<td>25(30.5%)</td>
<td>0.48</td>
</tr>
<tr>
<td>ARB</td>
<td>5(22.7%)</td>
<td>20(24.4%)</td>
<td>0.87</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>6(27.3%)</td>
<td>21(25.6%)</td>
<td>0.87</td>
</tr>
<tr>
<td>Thiazide</td>
<td>7(31.8%)</td>
<td>22(26.8%)</td>
<td>0.64</td>
</tr>
</tbody>
</table>

Note: ACEI = angiotension converting enzyme inhibitor, ARB = Angiotension receptor blocker.

### Table 4. Multivariate logistic regression analysis of associated factors in hypertensive CKD patients with PAD

<table>
<thead>
<tr>
<th>Variables</th>
<th>B</th>
<th>S.E.</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCB therapy</td>
<td>-1.461</td>
<td>0.590</td>
<td>0.232</td>
<td>0.073-0.737</td>
<td>0.013</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>0.062</td>
<td>0.020</td>
<td>1.064</td>
<td>1.024-1.106</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Note: 1. CI = Confidence interval, CCB = Calcium channel blocker.
2. Adjustment with age, diabetes, smoking, and gender.
Use Evaluation (VALUE) trial revealed that the primary outcome measure of cardiac morbidity and mortality was not significantly different between patients with PAD treated with ARB (valsartan) and calcium channel blockers (amlodipine)\textsuperscript{28}. The Invest (International Trandolapril study) Trial showed that the combination of ACEI with calcium channel blockers (CCB) was associated with fewer adverse outcomes than ACEI with a beta-blocker\textsuperscript{29}.

Class-specific selection of anti-hypertensive drugs in PAD should be based on co-existing disease and risk factors. The impact of BP control on PAD and cardiovascular events among patients with CKD has not specifically been studied\textsuperscript{30}. According to previous studies, we could only presume that ACEI, ARB and CCB use may reduce the risk of cardiovascular events in CKD patients with PAD. We could not determine whether these drugs could prevent PAD progression. There were also rare studies discussing which class of anti-hypertension drugs could directly prevent or retard PAD formation in CKD patients.

In our study, the main CCB used was dihydropyridine, which dilates blood vessel and increase renal sodium and water excretion\textsuperscript{31}. CCB treatment demonstrated a negative correlation with ABI<0.9 (OR = 0.232, 95% CI = 0.07-0.73, \( p = 0.013 \)) by logistic regression. However, further prospective studies must be conducted to determine if CCB treatment may prevent PAD in hypertensive patients with CKD.

According to previously documented studies, ACEI or ARB may also prevent PAD in hypertension CKD patients. However, ACEI and ARB may cause a reduction of GFR and elevation of serum creatinine. In our study, we did not see a significant correlation between ACEI and ARB treatments, mostly due to a decreased use of ACEI and ARB in our patients with stage 3 to 5 CKD.

Strict BP control is crucial for patients with PAD. This may be extended to patients with CKD and dialysis patients, who usually require BP control for management of their renal and cardiovascular diseases. However, prospective randomized controlled studies in CKD patients are needed to obtain evidence for specific blood pressure classes of treatment to reduce PAD and to further decrease cardiovascular events.

**Conclusion**

PAD has a relatively high prevalence among patients with stage 3 to 5 CKD in our study, especially those with hypertension. This study suggests a negative correlation between CCB treatment and ABI<0.9 in CKD hypertensive patients. The study also demonstrates that over half of the PAD patients are asymptomatic. ABI measurements may be carried out routinely in these patients for early diagnosis and therapeutic management.

**References**

慢性腎臟病人的周邊動脈疾病盛行率和臨床相關因子

楊清評¹ 蔡金燕² 葉淑娟³

¹高雄市立民生醫院 腎臟內科
²阮綜合醫院 小兒科
³國立中山大學 護理管理所

摘要

慢性腎臟病(chronic kidney disease)的病人有動脈粥樣硬化和周邊動脈疾病(peripheral artery disease)增加的風險。在這個研究，我們研究了慢性腎臟病患者和周邊動脈疾病的相關風險因素，並且以Fukuda Vascular Screening system VaSera VS-1000™來檢查腳踝和腕上臂血壓比(ankle-brachial index)，若病人的腳踝和腕上臂血壓比例小於0.9則診斷為周邊動脈疾病。總共包括124名慢性腎臟病第3到5期的患者，慢性腎臟病分期是依據結石質量主動性(K/DOQI)分期，患者都尚未接受透析療法，且先前未被診斷有周邊動脈疾病。總共有22個(17.7%)參與研究者有周邊動脈疾病。較高的心臓收縮血壓，舒張血壓，及脈壓(pulse pressure)和周邊動脈疾病之間有較強的相關性。邏輯式回歸分析後，發現在高血壓的慢性腎臟病患者顯示了風險因素為脈壓，而鈣離子阻斷劑治療在高血壓的慢性腎臟病患者，跟腳踝和腕上臂血壓比例<0.9有負相關(odds ratio = 0.232, CI = 0.07-0.73, p = 0.013)。研究發現周邊動脈疾病在慢性腎臟病患者有較高的盛行率，特別是那些合併有高血壓的患者。腳踝和腕上臂血壓比例(ABI)的檢查也許可以常規的使用在慢性腎臟病患者，使慢性腎臟病患者能獲得及早治療周邊動脈疾病的益處。