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 65.16 $\pm$ 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*

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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 $\geq$ 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.

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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;

ABI = 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 $\geq$ 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 $\pm$ 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 abnomal 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 non-smokers. 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

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

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

Stage	Odd ratio	95% CI
2	1.6	0.3-8.1
3	2.5	0.5-12.1
4	5.4	1.1-27.4
5	5.7	1.1-30.4

lower diastolic blood pressure. There were also a trend to increase in abnormal ABI rate in diabetic and CAD patients. Prevalence of asymptomatic PAD in CKD patients in our study was 22.4%.

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)

Fig. 1 The prevalence of abnormal ABI in the stage of chronic kidney disease (defined by ABI ≤ 0.9)

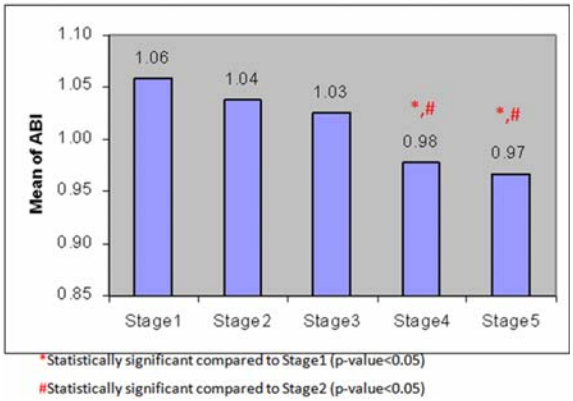

Fig. 2 Mean of ABI in CKD

but less than the study by de Vinuesa et al in subclinical peripheral arterial disease in patients with chronic kidney disease (32%)[12]. Although it could be associated with a lesser coexistence of risk factor of atherosclerosis such as male sex and smoking in our study more patients had diabetes and dyslipidemia. Another reason was that their study included symptomatic PAD (30% had sign and symptoms compatible with intermittent claudication), while our study excluded this factor.

ABI measurement is a simple and reproducible diagnostic tool with no inter-observer variation. So, it may be an appropriate method to detect and follow up atherosclerotic patients. Abnormal ABI might be used as a surrogate marker of atherosclerosis in CKD patients because the prevalence of abnormal ABI paralleled with the stage of CKD.

In the future, we recommend a longer duration of study and a greater number of patients because, in our study, sample size of each stage was different and 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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ความสัมพันธ์ของการเกิดโรคหลอดเลือดแดงส่วนปลายในแต่ละระยะของโรคไตวายเรื้อรัง

พวงผกา อึ้งประเสริฐ, สุวัจชัย พรรัตนรังสี

ภูมิหลัง*: โรคหลอดเลือดแดง atherosclerosis เป็นโรคที่พบบ่อยในเวชปฏิบัติ โดยปัจจัยเสี่ยงที่สำคัญต่อการเกิดโรคได้แก่ โรคเบาหวาน ความดันโลหิตสูง ไขมันในเลือดสูง การสูบบุหรี่ รวมถึงโรคไตวายเรื้อรังด้วย อย่างไรก็ตาม ยังมีการศึกษาอยู่น้อยถึงความสัมพันธ์ระหว่างโรคหลอดเลือดแดงส่วนปลายกับโรคไตวายเรื้อรังในแต่ระยะของโรคไต การตรวจวัดความดันที่แขนเทียบกับขา หรือที่เรียกว่า เอบีไอ (Ankle brachial index, ABI) เป็นวิธีการตรวจที่มีความปลอดภัยสูง มีความไวและความจำเพาะต่อการวินิจฉัยโรคหลอดเลือดแดงส่วนปลายเป็นอย่างมาก*

วัตถุประสงค์*: ศึกษาหาความสัมพันธ์ของการเกิดโรคหลอดเลือดแดงส่วนปลายในผู้ป่วยโรคไตวายเรื้อรังในแต่ละระยะที่ยังไม่มีอาการหรืออาการแสดงของโรคหลอดเลือดแดงส่วนปลาย โดยใช้การตรวจวัดเอบีไอ (Ankle brachial index, ABI)*

วัสดุและวิธีการ*: ผู้ป่วยโรคไต 201 ราย ในแต่ละระยะที่มาตรวจที่คลินิกผู้ป่วยนอกของโรงพยาบาลศิริราช ที่ยังไม่มีอาการของโรคหลอดเลือดแดงส่วนปลาย จะถูกส่งไปตรวจวัดเอบีไอในการแบ่งระยะโรคไตจะใช้ตามแนวทางของเคโดกี K/DOQI classification ผู้ป่วยที่มีค่าเอบีไอน้อยกว่า 0.9 จะได้รับการวินิจฉัยว่าเป็นโรคหลอดเลือดแดงส่วนปลาย*

ผลการศึกษา*: ผู้ป่วยโรคไต มีอายุเฉลี่ย 65.16 $\pm$ 11.3 ปี เป็นผู้ชาย 55% มีค่าเอบีไอน้อยกว่า 0.9 อยู่ 22.4% โดยพบว่าผู้ป่วยที่มีค่า ABI ผิดปกติส่วนใหญ่เป็นผู้ป่วยที่อายุมาก, ผู้หญิง, ค่าความดันโลหิตไดแอสโตลิกต่ำ เมื่อเทียบกับผู้ป่วยที่มีค่า ABI ปกติ ($p = 0.002, < 0.001, < 0.0001$ เรียงตามลำดับ) โรคเบาหวาน และโรคหลอดเลือดหัวใจพบมากกว่าในผู้ป่วยที่มีค่า ABI ผิดปกติแต่ไม่มีนัยสำคัญทางสถิติ ปัจจัยทางคลินิกอื่นเช่น ความดันโลหิตสูง ไขมันในเลือดสูง การสูบบุหรี่ไม่พบว่ามีความแตกต่างกัน การตรวจพบ ABI น้อยกว่า 0.9 จะพบมากขึ้นตามระยะของโรคไต ผู้ป่วยโรคไตมีค่า ABI เฉลี่ยลดลงตามระยะของโรคที่มากขึ้นโดยระยะ 4 และ 5 มีค่าต่ำกว่าระยะที่ 1 และ 2 อย่างมีนัยสำคัญ ($p < 0.05$)*

สรุป*: โรคหลอดเลือดแดงส่วนปลาย (การตรวจเอบีไอได้น้อยกว่า 0.9) พบมากขึ้นในผู้ป่วยโรคไตวายเรื้อรังระยะท้าย*