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SM Journal of Nephrology and Kidney Diseases

Research Article

Peripheral Arterial Disease Holding Central Stage in Chronic Kidney Disease (Kdoqi Stage 3-5): Prevalance and Related Risk Factors-Experience from Kashmir Valley Teritary Care Centre

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Article Information

Received date: Sep 04, 2017
Accepted date: Oct 25, 2017
Published date: Oct 30, 2017

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Keywords PAD: Peripheral Arterial Disease; CKD: Chronic Kidney Disease; Atherosclerosis; IC: Intermittent Claudication

Article DOI 10.36876/smjnkd.1007

Abstract

Patients with CKD are highly predisposed for developing accelerated atherosclerosis. These patients have non-traditional risk factors such inflammation, malnutrition and increased oxidative stress that enhance and accelerate atherosclerosis in addition to traditional risk factors. Although relation between cardiovascular and cerebrovascular diseases with CKD is well established, studies are suggesting about association of Peripheral Arterial Disease (PAD) with CKD. PAD is associated with increased morbidity and mortality in patients of CKD.

This study is rendezvous to look for PAD and related risk factors in patients of CKD having eGFR less than 60 ml/ min/ 1.73 m^2 (MDRDS) and not on RRT.

Two hundred ten subjects with CKD attending department of nephrology at tertiary care institute in valley were included in study. Out of 210 subjects selected, 30 were having PAD that constituted 14% of study population. IC was seen in 25 (11.9%) of 210 subjects. Out of PAD patients 16 (53.3%) were having history of IC and 14 (46.7%) were asymptomatic. As reported in literature, prevalence of peripheral arterial disease in CKD patients not on dialysis ranged from 7% to 32% in previous cases. This study will sensitize us to plan more effective screening, preventive and management strategies. This will go long way to decrease morbidity and mortality in patients.

Introduction

Chronic kidney disease (CKD) encompasses a spectrum of different path- physiologic processes associated with abnormal kidney function and a progressive decline in Glomerular Filtration Rate (GFR). CKD is staged into five stages according to estimated GFR based on guidelines of national kidney foundation kidney disease outcome quality initiative (NKF/KDOQI) [1]. Two equations are used to estimate GFR (eGFR) i.e Modification of Diet in Renal Disease Study (MDRDS) and Cockcroft-Gault equation (Table 1) [2]. The normal peak GFR is attained during third decade approximately 120 ml/min/1.73 m^2 and thereafter declining annually at rate of 1ml/min/year/1.73 m^2 reaching mean value of 70ml/min/1.73 m^2 at age of 70 years [3].

In patients of CKD once GFR falls below 60 ml/min/1.73 m^2 i.e stage 3 or above, clinical and laboratory abnormalities become more pronounced. Once patients GFR falls below 15 ml/min/ 1.73 m^2 i.e stage 5 there is marked disturbance in body haemostasis which culminate in the uremic syndrome that may lead to death unless renal replacement therapy (dialysis or transplant) is instituted [4,5].

Peripheral Arterial Disease (PAD) is a clinical syndrome in which there is stenosis or occlusion in the aorta or arteries of limbs. Atherosclerosis is the leading cause of PAD followed by thrombosis, embolism, vasculitis, fibro muscular dysplasia, entrapment, cystic adventitial disease and trauma [6]. It is defined as Ankle Brachial Index (ABI) of less than 0.9; it has sensitivity of 95% and specificity of 100% for angiographically documented PAD for arterial stenosis >/= 50% in the lower extremities [7,8]. Around 50% of patients are asymptomatic. Most common symptom is Intermittent Claudication (IC) - muscle discomfort in lower limbs reproducibly produced by exercise and relieved at rest within 10 minutes usually distal to occlusive lesion; with severe ischemia pain may be persistent. There may be ulceration and gangrene in distal extremity [6]. There are number of scoring systems for claudication, Edinburg Claudication Questionnaire (ECQ) - an improved version of WHO/ROSE QUESTIONNAIRE has got high sensitivity (93.1%) and specificity (99.3%) compared to diagnosis of physician [9]. The prevalence of PAD in patients can be estimated best with non invasive measurement of ABI by sphygmomanometer and Doppler instrument [7]. This

OPEN ACCESS
ISSN: 2576-5450

is done by measuring systolic blood pressure in posterior tibial or dorsal pedis artery and normalizing these with higher brachial artery blood pressure. A reduced ABI in symptomatic patients confirms the existence of hemodynamically significant occlusive disease between heart and the ankle, with lower ABI indicating a greater hemodynamic severity of occlusive disease.

Patients with CKD are highly predisposed for developing accelerated atherosclerosis. Not only these patients have increased prevalence of traditional risk factors of cardiovascular diseases such as hypertension, diabetes, dyslipidemia and smoking but they also have non-traditional risk factors such inflammation, malnutrition and increased oxidative stress that enhance and accelerate atherosclerosis [10-14].

Although relation between cardiovascular and cerebrovascular diseases with CKD is well established, there are few studies about its association with PAD from this part of world. PAD is associated with increased morbidity and mortality in general population and more so in patients of CKD [15,16].

It is prudent to know prevalence of PAD in CKD patients and its related risk factors in our region so as to initiate appropriate diagnostic and management strategies that would result in reduction of morbidity and mortality in this group of patient.

Material and Method

This study was conducted to know prevalence of PAD in CKD and related risk factors at tertiary care institute of Srinagar after taking clearance from ethical committee of institute. Informed consent was taken from patients for participation in study. Of the 210 subjects with CKD, fulfilling the below mentioned inclusion /exclusion criteria that were admitted in the department of nephrology or attending OPD clinic were included in study.

Inclusion criteria

1. Patient more than 19 years of age and less than 95 years of age.
2. Pre-dialysis with eGFR less than 60 ml/min/ 1.73 m^2 (stage 3 to 5 CKD). GFR was estimated with MDRDS [2].

Exclusion criteria

1. Extreme of ages.
2. eGFR greater or equal to 60 ml/ min.
3. CKD patients on dialysis either hemodialysis or peritoneal dialysis.
4. Post transplant patient.
5. Patient with solitary kidney.

Methodology

In all subjects (patients) of CKD thorough history was taken, their medical record checked and physical examinations was done. We took history of related risk factors like smoking, hypertension, diabetes, CAD, CVD and dyslipidemia. Baseline and other relevant investigations were repeated.

All selected subjects were administered Edinburg Claudication Questionnaire of claudication in PAD. This questionnaire involves total six questions; we proceed further once answer to first question is affirmative.

1. Do you get a pain or discomfort in your leg(s) when you walk?

   ☐ Yes ☐ No ☐ I am unable to walk

   If you answered "Yes" to question (1), please answer the following questions.

   Otherwise, you need not continue.

2. Does this pain ever begin when you are standing still or sitting?

   ☐ Yes ☐ No

3. Do you get it if you walk uphill or hurry?

   ☐ Yes ☐ No

4. Do you get it when you walk at an ordinary pace on the level?

   ☐ Yes ☐ No

5. What happens to it if you stand still?

   ☐ usually continues more than 10 minutes.

   ☐ usually disappears in 10 minutes or less.

6. Where do you get this pain or discomfort? i.e on front/ back of lower limbs.

   Definition for positive classification requires:

   • No to question 2,

   • Yes to question 3,

   • Usually disappears in 10 minutes or less for question 5.

After questionnaire, ABI is estimated in all the study subjects using portable pulse detector (Ultrasonic Mini Doppler Hi.dop; Bistos Co, Ltd; Made in Korea) and an 8 MHz probe. Diamond blood pressure apparatus with 12 cm cuff. Measurements were made after 5 minutes of rest in supine decubitus position. ABI is calculated as below:

ABI = Posterior Tibial Systolic Blood Pressure (mmHg) (lower one)

Brachial Artery Systolic Pressure (mmHg) (higher one)

Table 1: Formulas for estimation of GFR.

1	**MDRD**	Abbreviated MDRD equation = 186 × ($SCr^{-1.154}$) × ($age^{-0.203}$)
2	**Cockcroft-Gault equation**	eGFR (mL/min) = 140-age) × Body weight (kg)/72 × PCr (mg/dl)

Note: Weight in kilograms, age in years. Estimated Glomerular Filtration (eGFR) rate expressed in mL/min. (1) Multiply by 0.742 if female, by 1.212 if African American; expressed in mL/min/1.73 m^2. (2) Multiply by 0.85 if female; expressed in mL/min. MDRD-modification of diet in renal disease; SCr-serum creatinine level, expressed in mg/dL.

Citation: Mir MM, Najar MS, Sharma BK, Singh M, Mir UT and Rather MK. Peripheral Arterial Disease Holding Central Stage in Chronic Kidney Disease (Kdoqi Stage 3-5): Prevalance and Related Risk Factors-Experience from Kashmir Valley Teritary Care Centre. J Nephrol Kidney Dis. 2017; 1(2): 1007. https://dx.doi.org/10.36876/smjnkd.1007

Table 2: IC correlation with ABI.

ECQ	ABI LEVELS <0.9	>/=0.9 to 1.3	>1.3	total	*p*-value
No	16 53.30%	153 93.30%	16 94.10%	185 88.10%	
Yes	14 46.70%	10 6.10%	1 5.90%	25 11.90%	
total	30 100%	163 100%	17 100%	210 100%	<0.0001

The index leg is often defined as leg with lower ABI. ABI is graded as per ACCF/AHA Focused Update of the Guideline for the Management of Patients with Peripheral Artery Disease [17]. ABI results are reported as:

1. Non-compressible values defined as greater than 1.40,
2. Normal Values - 1.00 To 1.40,
3. Borderline - 0.91 to 0.99 and
4. Abnormal - 0.90 or less.

Stastical Analysis

Results were recorded as median +/- standard deviation. Chi square and Fisher's exact test were used for categorical and ANOVA techniques along with posthoc and krusskall walis test were used for continuous variables. SPSS software version. P values less than 0.05 are significant.

Observations

This study was conducted to know prevalence PAD in CKD patients not on Renal Replacement Therapy (RRT) presenting to department of nephrology in our region.

Of 210 subjects enrolled 133 (63%) were males and 77 (37%) were females. Of 30 subjects having PAD 19 (63.3%) were males and 11 were females (36.7%). This difference was not significant. Age of subjects ranged from 21 to 95 years with mean age of 52.31+/- 14.95. Mean age of subjects having PAD was 63.83 +/- 9.4 years, were as those having ABI > 0.9 was 50.36 +/- 14.82 years signifying elderly CKD subjects are more likely to have PAD (*P*=0.003). Average eGFR was 16 +/- 10.20 ml/min, of whom 20 (9.5%) were stage 3, 88 (41.9%) were stage 4 and 102 (48.6%) were stage 5. Most of our patients had advanced renal disease. Of 30 CKD patients having PAD, mean eGFR was 15.97 +/- 10.14 ml/min 1.73 m^2.

In our patients; 14% were having PAD i.e 30 patients had ABI < 0.9. Of those 30, 16(53.3%) were having history of IC, whereas 14 (46.7%) were asymptomatic for PAD. Out of remaining 163 subjects having ABI >/= 0.9 -1.3, only 10 (6.1%) subjects was having IC. Out of 17 subjects with ABI > 1.3, 1 (5.9%) was having IC. Thus IC is strongly suggestive of PAD (*p*<0.0001) (Table 2). Mean eGFR was 15.97 +/- 10.14 ml/min 1.73 m^2. Two subjects (6.7%) had stroke. Mean Body Mass Index (BMI) of patients with PAD was 23.2 +/- 3.14; calcium phosphorus product in patients with PAD is 42.95 +/-13.55. These parameters did not vary significantly between PAD and non PAD subjects.

All CKD patients having PAD were hypertensive, 18 (60%) were diabetic, mean serum albumin of PAD patients was 3.49+/- 0.62 mg/dl, 7 (23.3%) were having dyslipidemia, 9 (30%) were having CAD and 7 (23.3%) were active smokers and 12 (40%) were ex-smokers. All these parameters have significant association with CKD i.e *p* value less than 0.05 on univariate analysis (Table 3). However on applying binary logistic regression analysis on data we found that symptoms of intermittent claudication as assessed by ECQ were strongly associated with PAD (*p* value is < 0.001) and CAD (*p* value is <0.001).

Table 3: Observations.

N	Parameter	PAD (n=30) ABI:<0.9	NON-PAD (n=180) ABI: 0.9-1.3	ABI:>1.3	*p*-VALUE
1	Male	19(63.3%)	101 (62%)	13 (76%)	
2	Female	11(36.7%)	62 (38%)	42 (3.5%)	0.498
3	Age	63.83±9.4 years	50.36±14.82 years	50.65±15.652 years	<0.001
4	A, smoker	7 (23.3%)	44 (27.0%)	2 (11.8%)	
	B, ex-smoker	12 (40%)	29 (17.8%)	6 (35.3%)	0.039
5	Dyslipidemia	7 (23.3%)	13 (8.0%)	3 (17.6%)	0.031
6	Bmi	23.2 +/- 3.14	23.06 +/- 2.32	22.97 +/- 2.60	0.981
7	Ecq	14 (46.7%)	10 (6.1%)	1 (5.9%)	<0.0001
8	Mean egfr ml/min	15 +/- 10.14	17.47 +/- 10.93	13.76 +/- 8.94	0.632
9	Albumin (mg/dl)	3.49 +/- 0.62	3.60 +/- 0.51	3.89 +/- 0.49	0.044
10	Calcium (mg/dl)	8.53 +/- 0.77	8.22 +/- 0.84	8.37 +/- 1.30	0.201
11	Phosphorus (mg/dl)	5.08 +/- 1.72	4.90 +/- 1.79	5.73 +/- 1.99	0.194
12	Diabetes	18 (60%)	44 (27%)	3 (17.6%)	0.001
13	Hypertension	30 (100%)	139 (85.3%)	12 (70.6%)	0.015
14	Cad	9 (30%)	4 (2.5%)	0 (0.0%)	<0.0001
15	Stroke	2 (6.7%)	2 (1.2%)	0 (0.0%)	0.112

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Discussion

Patients with CKD are predisposed for developing accelerated atherosclerosis even in absence of certain traditional cardiovascular risk factors. Although relation between cardiovascular and cerebrovascular diseases with CKD is well established, also there are studies about association of CKD with Peripheral Arterial Disease (PAD) in patients on RRT; however few studies on PAD in CKD patients not on RRT. Our study was a rendezvous to look for PAD in CKD patients especially those having eGFR less than 60 ml/ min/ 1.73 m^2 and not on RRT and its related risk factors. As PAD is associated with increased morbidity and mortality in general population and more so in patients of CKD [11,12].

We conducted this study at our institution to know the prevalence of peripheral arterial disease in CKD not on RRT patients in our region. We enrolled 210 subjects presenting to us over period of one year (2014-2015). Mean age of our subjects was 52.31 +/-14.9 years ranging from 21 years to 95 years. Of 210 subjects 63% were males and 37% were females. Majority patients were from Srinagar district (33%) [13-17].

In our study, out of 210 subjects selected, 30 were having PAD that constituted 14% of study population. As reported in literature, prevalence of peripheral arterial disease in CKD patients not on dialysis ranged from 7% to 32% in previous cases.

Fu-An Chen et al (2012) [18] studied ABI as predicator of renal outcome and cardiovascular events in patients of CKD and enrolled 436 subjects with mean age of 73.4 +/- 10.5 years, 36.9% were diabetic, 87.4% were hypertensive. They reported prevalence of low ABI as 12.4% and mean estimated GFR of 28 +/- 13 ml/ min/1.73m^2, result is more or less comparable to our study. Angeles Guerrero et al in 2006 [19] studied 73 subjects with stage 4 and 5 CKD for presence of PAD. Mean age of population was 58 +/-15 years and estimated eGFR was 18.6 +/-6.1 ml/min. They found prevalence of PAD in CKD of 19 %. Soedad Garcia De Vinuesa et al (2005) [20] from Madrid Spain reported prevalence of 32% in their study that is much higher than ours. They enrolled 102 subjects with mean age of 70 +/- 11 years (58 to 84 years) with estimated GFR of 35 +/- 12 ml/ min/1.73m^2. Prevalence was higher in this study than ours as patients were in higher age group; in our study patients were younger with mean age of 52.31 +/-14.9 years. Joachim H. Ix et al [21], Shlipak MG et al [22], Lash JP et al [23] and Selvin E et al [24] reported prevalence of 13%, 12%, 15.9% and 24% respectively.

In our study, mean age of subjects having PAD was 63.83 +/- 9.4 years signifying elderly CKD subjects are more likely to have PAD (P=0.003). Angeles Guerrero et al in 2006 [19] noted patients with PAD were elder (p was 0.000) and lower GFR (p was 0.016). Selvin E, Erlingar TP in 2004 [24] reported increased prevalence of PAD in patients of higher age group. Joachim H Ix et al [21] studied association with spectrum of ABI in four communities in USA and reported higher prevalence of lower ABI with increasing age.

In our study, all subjects having PAD were hypertensive (p=0.015), 18(60%) were diabetic (p=0.001), mean serum albumin was 3.49+/- 0.62 mg/dl (p=0.044), 7(23.3%) were having dyslipidemia (p=0.031), 9(30%) were having CAD (p<0.0001) and 7 (23.3%) were active smokers and 12 (40%) were ex-smokers (p=0.039). All these parameters have significant association with CKD i.e p value less than 0.05 on univariate analysis (Table 3). Chen SC et al (2008), Fu-An Chen et al (2012) found positive association between hypertension and PAD in CKD patients with p value of < 0.005 and 0.002 respectively. Angeles Guerrero et al in 2006 [19] found significant association of PAD with diabetes (p value of 0.001) and CAD (p value of 0.001) in CKD patients. Soedad Garcia De Vinuesa et al (2005) [20] and Mostaza JM et al (2006) [25] found significant association of PAD with smoking (p value of 0.02) and diabetics (0.05) in patients of CKD. Mostaza JM et al (2006) [25] and Chen SC et al (2008) [26] found significant association of PAD and albuminuria in CKD patients with p value of 0.001 and 0.009 respectively. Mostaza JM et al (2006) [25] found significant association of PAD and hypertriglyceridemia in CKD patients with p value of 0.001. Angeles Guerrero et al in 2006 [19] and Soedad Garcia De Vinuesa et al (2005) [20] found no significant difference in lipid profile of their CKD patients with or without PAD.

In our study there was no significant difference for PAD in terms of eGFR. While analysing our data we found our patients were of younger age group (mean age of 52.31+/- 14.95) than many other studies and also eGFR was also lower (average eGFR was 16 +/- 10.20 ml/min), of whom 20 (9.5%) were stage 3, 88 (41.9%) were stage 4 and 102 (48.6%) were stage 5. Most of our patients had advanced renal disease (90.87%). So simply, inter group univariate analysis did not yield statistically significant results, although Angeles Guerrero et al in 2006 also reported similar result. However Mostaza JM et al (2006) [25], Joachim H Ix et al [21], Shlipak MG et al [22], Lash JP et al [23] and Selvin E et al [24] reported low eGFR independently associated with PAD but these studies have mean eGFR was much higher than in our study.

Summary

Although relation between cardiovascular and cerebrovascular diseases with CKD is well established, there are few studies about its association with PAD this part of world. PAD is associated with increased morbidity and mortality in general population and more so in patients of CKD.

Our study is in pursuit to look for PAD and associated risk factors in those patients of CKD having eGFR less than 60 ml/ min/ 1.73 m^2 and not on RRT.

Prevalence of PAD in CKD is high, 14% in our study population. Out of PAD patients 16 (53.3%) were having history of IC and 14 (46.7%) were asymptomatic. Symptoms of intermittent claudication are highly suggestive of PAD and should prompt us to look for it. Smoking, hypertension, diabetes, CAD, low serum albumin, dyslipidemia all are more commonly associated with CKD patients having PAD, how much these contribute to development of PAD cannot be said.

This study will sensitize us to plan more effective screening, preventive and management strategies that will go long way to decrease morbidity and mortality in this group of patient.

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