PERIPHERAL ARTERIAL DISEASE IN CHRONIC KIDNEY DISEASE PATIENT

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Abstract

Among the different complications of chronic kidney diseases, Peripheral Arterial Disease (PAD) is not uncommon which is an indicator of wide spread atherosclerosis in other vascular territories, such as the cerebral and coronary circulations. Traditional cardiovascular risk factors, such as black race, male gender, age,tobacco use, diabetes, hyperlipidemia, and hypertension are also associated with PAD. But in kidney patients this disease is sometimes neglected. This present review tends to describe epidemiology, risk factors and necessities for screening of PAD in chronic kidney disease patients.

Key words

Chronic kidney disease; Peripheral arterial disease; Atherosclerosis.

Introduction

Cardiovascular disease in patients with Chronic Kidney Disease (CKD) is common and has major implications in terms of both human suffering and health economics. Individuals with CKD are at increased risk for Cardio Vascular Diseases (CVD) which include specific conditions such as Coronary Artery Disease (CAD) Congestive heart failure and PAD. Among the different localizations of CVD, PAD affecting the lower limbs has a higher morbidity. This is an indicator of wide spread atherosclerosis[1]. There is also considerable overlap between PAD, Cerebro Vascular Disease (CBVD) and CAD with the presence of PAD being associated[2-4]. PAD is measured by an Ankle-Brachial Index (ABI). The population with CKD is particularly at risk for PAD, that accounts for significant morbidity and mortality among End Stage Renal Disease (ESRD) patients with a prevalence of 24% in one cross-sectional analysis[5,6]. Due to a lack of consensus regarding treatment options and the poor outcomes associated with traditional surgical revascularization and amputation for the ESRD population, screening for PAD remains a controversial topic[7]. However, there is evidence that supports aggressive screening, diagnosis, medical treatment, and revascularization prior to amputation to reduce mortality. Non-surgical interventions are available to re-establish circulation to the lower extremities, thereby decreasing or resolving symptoms associated with PAD such as claudication and skin ulceration[8]. Nephrology professionals understand how an amputation can impact the prognosis for effective dialysis. Therefore, nephrologists must have knowledge about screening, diagnosis, and treatment strategies for this condition.The latest Inter-Society Consensus for the Management of PAD (TASC II) guidelines recognized CKD asa risk factor for PAD[9]. This was largely based on findings of the Heart and Estrogen/Progestin Replacement Study (HERS) in which CKD was found to be independently associated with PAD in postmenopausal women. For the nondialysis patient with PAD, 1 to 3% with claudication will undergo an amputation in 5 yr[9]. Among patients with ESRD, amputation for PAD is more prevalent compared with the general population[10]. The incidence of PAD increases with age. Data from the National Health and Nutrition Examination Survey (NHANES) reveals that the prevalence of PAD in the age group 50 to 59 yrs is 2.5% and increases to 14.5% in the age group of 70 yrs. Patients with impaired renal function have a greater than two-fold risk for developing PAD[11].

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The NHANES 1999–2000 found 24% of adults who were older than 40 yrs and had a creatinine clearance ≥60ml/min per 1.73 m2 to have an ABI of ≥0.9[9]. In the dialysis population, according to United States Renal Data System report,the incidence of clinical PAD is 15%[12].

Traditional cardiovascular risk factors, such as tobacco use,diabetes, hyperlipidaemia, and hypertension, are also associated with PAD. Unmodifiable risk factors that are associated with PAD include black race, male gender, and age. Of the modifiable risk factors for PAD in the general population, tobacco abuse is likely the most important[13]. The prevalence of PAD among those with diabetes is high, and many people's diabetes is undiagnosed[14]. Dyslipidemia plays an important role in the pathogenesis of atherosclerosis and is strongly associated with PAD. Recently, the Ankle–Brachial Index (ABI) has been recognized as an accurate and reliable marker of sub-clinical or clinical PAD[15]. ABI is a non-invasive test to screen for PAD, measured by a hand-held Doppler probe, and is the ratio between systolic Blood Pressure (BP) in the ankle and systolic BP in the arm. Measurement of ABI has shown high sensitivity (95%) and specificity (100%) for the diagnosis of PAD in comparison with arteriography, the gold standard[16]. The normal value of the ABI ranges from 0.9 to 1.4. On the basis of epidemiological evidence, current guidelines recommend a cut-off of 0.9 for the diagnosis of PAD[17].

The study regarding evaluation of peripheral arterial disease in CKD patient in developing country is even scarse. So this present study is aimed to evaluate the prevalence and pattern of peripheral arterial disease globally as well as some data in developing country.

Search Strategy

PubMed search with clinical query was done with key wards (PAD AND CKD) AND Atherosclerosis AND Developing country. References of the main articles were also searched.

Discussion

Despite the high prevalence of PAD and the increased risk of mortality and morbidity of cardiovascular diseases in individuals with PAD, it is still under diagnosed and undertreated because of lack of symptoms, subtly of clinical findings, and lack of awareness. Three out of four people are not aware of PAD and few Americans know that having PAD significantly increases the risk for heart attack and stroke[18]. Diagnosis of PAD is essential to improve quality of life, prevent further functional impairment, and to reduce cardiovascular disease mortality and morbidity.

Epidemiology

The prevalence of PAD differs widely depending on the population, the diagnostic tool used and the methods of the study. In general PAD affects 4% to 12% of people aged 55-70 years and 15-20% of people aged over 70 years[19]. In the United States, PAD affects approximately 8 million adults over the age of 40. The incidence of PAD increases substantially with age in both sexes at a rate of 1.5 to 2 fold for every 10 year increase in age. PAD affects 4 percent of people 40 years of age or older, however, the prevalence increases to 14.5 percent at age 70[19]. The prevalence of PAD is 25 to 30% among people with multiple risk factors in primary care settings[20]. There is no substantial difference in PAD incidence between men and women, never the less, African-Americans have a 2.4 fold increase in prevalence than the non-Hispanic white population[19,20]. Individuals with PAD are at a 3 times increased risk for all cause mortality compared with the general population.

Also, they are 6 times more likely to have a heart attack and 2 to 3 times more likely to have a stroke with in the next 10 years[21]. The cost of PAD-related treatment was 4.37 billion dollars in the medicare population, however, this is not including the undiagnosed people[22]. According to a report published in 2004 by the Sage Group out of Atlanta, approximately 160,000 amputations are performed annually in the United States because of PAD[23]. Depending on the patient population, procedural mortality rates range from 4% to 30% and morbidity from 20% to 37%. In developint countries data is incomplete[5].

Risk Factors

Smoking

Smoking is probably the most important risk factor for PAD. Cigarette smoking increases the risk of PAD by 7 fold. Smoking is associated with PAD more strongly than CAD. Smoking also reduces the effectiveness of anti-platelet medication in such patients[24,25]. CRP, fibrinogen and homocysteine are novel risk factors in both white and non-white ethnic groups[26].

Diabetes

Diabetes is another major risk factor for PAD and its complications. PAD is twice more common among patients with diabetes than non-diabetic patients. Because it is accompanied with peripheral neuropathy (Decreased sensation in the extremities especially legs and feet) the symptoms of PAD among patients with diabetes are often more subtle and the classic intermittent claudication (Pain that occurs with walking and usually improves with rest) is less common. Foot ulcerations, infection, and gangrene may be the initial presentation of peripheral arterial disease among patients with diabetes. PAD in patients with diabetes are usually more diffuse and distal[27]. Insulin resistance is also a risk factor for PAD even in individuals without diabetes[28].

Dyslipidaemia

The ratio of Total Cholesterol (TC): High Density Lipoprotein Cholesterol (HDL-C) is the strongest lipid predictor of PAD risk[29]. The most frequent dyslipidaemia associated with PAD is elevated triglycerides and low HDL-C[30]. LDL should be the primary target for lipid control with value of 1.8 mmol (Or 50% reduction from the initial value in very high risk patients) and 2.6 mmol/l in high risk patients. According to the ESC Guidelines 2016 every CKD with GFR 30-59 ml/min/1.73 m^2 or PAD is a high risk patient. Very high risk patient is the one with GFR <30 ml/min/173 m^2 or CKD with history or documentation of PAD or coronary artery disease[31].

Hypertension

Hypertension is a major risk factor for all vascular disorders and is associated with a 2- to 3-fold risk for PAD[1]. 2 to 5% of hypertensive patients have intermittent claudication, while 35 to 55% of patients with PAD at presentation have hypertension. Low HDL-C is closely linked to the development of PAD[1,32].

Homocysteine

Clarke et al were the first to report that hyperhomocysteinaemia could be an independent risk factor for atherosclerosis[33]. Homocysteine has been thought to be associated with thrombotic events although the precise mechanisms by which elevated homocysteine levels contribute to the pathogenesis of vascular disease are unknown.

Obesity

Obesity is also an important risk factor for developing PAD. Increased waist to hip ratio of more than 0.966 (Median value) was found to be independently associated with PAD. In studies, it was found that Body Mass Index (BMI) did not correlate with PAD after controlling for smoking, diabetes, hypertension, high-density lipoprotein cholesterol, and triglycerides[34]. Obesity leads to worsening of intermittent claudication, physical function, and health-related quality of life in the individuals with PAD.

The fontaine classification describes PAD as follows [29] :

Stage I -Asymptomatic

Stage II -Intermittent claudication

Stage III -Rest pain / Nocturnal pain

Stage IV -Necrosis / Gangrene

Establishing the diagnosis of PAD in CKD

The main method to confirm the diagnosis is Doppler ultrasonography (Duplex scanning). The ratio of systolic blood pressure at the ankle and in the arm Ankle-Brachial Pressure Index (ABPI) provides a measure of blood flow at the level of the ankle. The ABPI is a strong marker of cardiovascular disease and is predictive of cardiovascular events and mortality[35].

Status of peripheral artery according to ABI

Range of ABI	Condition of Artery
> 1.4	Calcification/ Vessel Hardening
1-1.4	Normal
0.9-1	Border Line
0.8-0.9	Some Arterial Disease
0.5-0.8	Moderate Arterial Disease
< 0.5	Severe Arterial Disease

Duplex ultrasonography is also able to determine the site of disease and indicate the degree of stenosis and length of an occlusion.Other methods of investigation now include MR angiography and CT angiography. MR angiography may be offered prior to revascularization[36]. Digital subtraction arteriography is not recommended as the primary

imaging modality and is essentially a pre-operative investigation. Its use is limited to an adjuvant of endovascular management, surgical planning or the management of an acute ischaemic limb.

Box 1 : Screening for peripheral arterial disease in CKD[37]

Recommendations for detection of PAD in clinical practice KDOQI

- At the time of dialysis therapy initiation, all patients should be evaluated for the presence of PAD
- Evaluation should include physical examination, including assessment of arterial pulse
- Further specialized studies, such as duplex studies or invasive testing, should be under taken if abnormalities are detected upon physical examination and if interventions are considered.

TASC II

Recommend screening for PAD in:

- Patients with exertional leg symptoms
- Patients aged 50–69 years with cardiovascular risk factors
- All patients aged ≥70 years
- Pts with a 10-y risk of a cardiovascular event of 10-20%, determined by SCORE / Framingham

ACC/AHA

Recommend screening for PAD in:

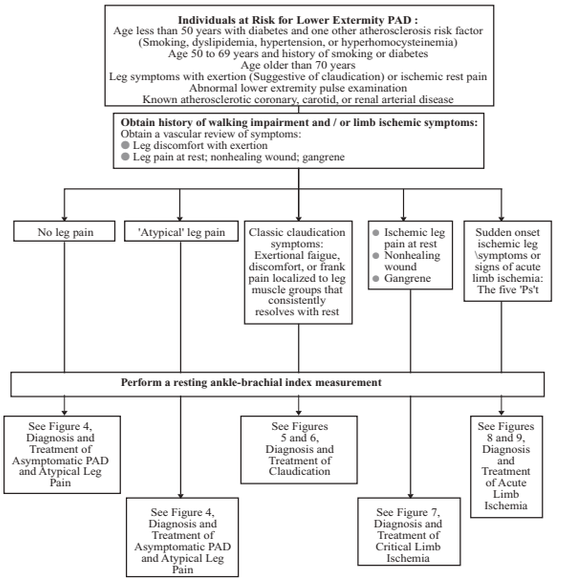
- Patients aged <50 y with diabetes and additional CVD risk factor
- Patients 50 years with any CVD risk factor (Smoking, diabetes, hypertension, elevated cholesterol)
- Patients 65 ≥ years.

KDOQI= National Kidney Foundation
TASC=Inter-Society Consensus of Treatment of PAD
ACC=American College of Cardiology
AHA=American Heart Association

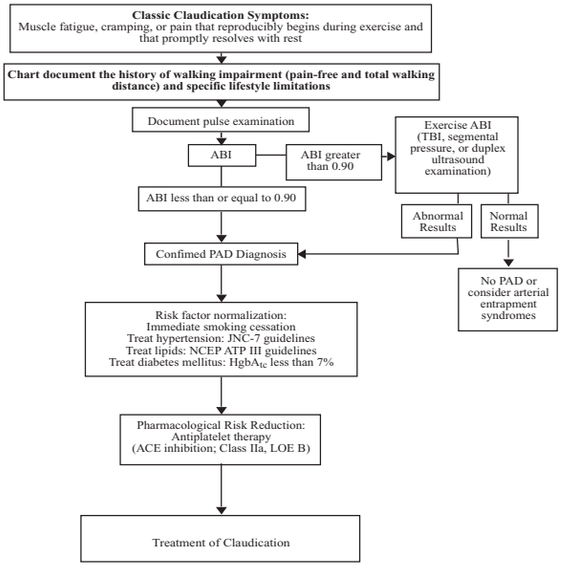
Combined effect of chronic kidney disease and peripheral arterial disease on mortality in a high-risk population

CKD and PAD are independent predictors of mortality. The overall 6 years mortality ratein a study of peripheral arterial disease and the CKD Patient. The case for early screening, diagnosis and minimally invasive revascularization in USA was 28% (n = 284). Patients with PAD and CKD had the highest 6 years mortality rate at 45%. Patients with CKD alone had a 28% mortality rate. Patients with PAD alone had a 26% rate. Patients with neither condition had an 18% mortality rate[38].

Algorythm 1: ACC-AHA PAD Guideline algorithm defining the key clinical PAD syndromes that define subsequent care pathways[39]



Algorythm 2: The ACC-AHA PAD Guideline algorithm for the treatment of claudication[39]



Current KDIGO guidelines recommend that adults with CKD at risk for atherosclerotic events be offered treatment with an antiplatelet medication (Usually low dose aspirin or clopidogrel) unless there is an increased bleeding risk that needs to be balanced against the possible cardiovascular benefit.

Secondary prevention of CVD in patients with PAD (With or without CKD)[39]

Recent KDOQI Guidelines on the management of diabetes in CKD have however recommended a goal HbA1C of 7% in persons with CKD and higher goals in those at risk of hypoglycemia or those with significant co-morbidities and limited life expectancy.

Due to their cardio-protective benefit, ACE-I and ARB medications are considered indicated for patients with PAD in current care guideline Beta-blocker use is not contraindicated in persons with CKD or claudication, as there is no detrimental impact on claudication symptoms or limb outcome given the high PAD and CAD disease burden in patients with kidney disease, statin use may be reasonable until conclusive evidence suggests otherwise.

Collaborative care opportunities to improve PAD-CKD care delivery[39]

Focus Area	Suggestions for Nephrologists	Suggestions for Vascular Specialists
Claudication Care Improvement	Recognize both classic claudication and atypical leg pain symptoms in patients with CKD. Become adept at interpretation of PAD non-invasive vascular laboratory diagnostic tests. Utilize the claudication medication, cilostazol, with appropriate dose adjustment in patients with PAD and claudication (No PAD anatomic imaging required) Create and utilize supervised exercise as a primary claudication therapy in individuals with PAD and CKD (no PAD anatomic imaging required) Referral to vascular specialist when revascularization is required (Failure of medical claudication therapies).	Provide full range of claudication therapies to individuals with PAD and CKD and claudication. Provide appropriate dose adjustment of cilostazol for patients with CKD and ESRD. Co-lead creation of PAD claudication supervised exercise programs to assure that this modality is available Co-manage diabetes, lipids and hypertension, promote smoking cessation, antiplatelet therapy.
Amputation Prevention (CLI care) Improvement	Active surveillance for PAD and CLI, via provision of foot examinations and evaluations for neuropathy, pedal perfusion, and foot deformities, especially in dialysis patients. Engagement of wound care nurse or podiatry services in dialysis unit on a scheduled basis.	Promote appropriate use of the noninvasive vascular laboratory, and use of physiologic (Non-contrast) testing, and TBI/duplex techniques in patients with normal or supranormal ABI values, especially when clinical suspicion is high. Co-develop an amputation prevention program to assess feet and wounds at regular intervals at affiliated renal clinics and dialysis units.
Clinical Research Improvement	Build health system, regional or national registries of CKD patients with PAD in order to define real world outcomes, clinical failures, and to provide a platform to objectively test new care strategies. Use this platform to provide pilot data to inform PAD-CKD observational studies and prospective randomized clinical trials. ● Create a new PAD risk model to help identify CKD patients at high risk ● Evaluate the accuracy of current PAD diagnostic testing strategies in CKD cohorts ● Prospectively test the impact of diagnostic testing, medical, and invasive care strategies to prevent adverse CVD and limb outcomes ● Refer to and enroll patients with CKD into current clinical trials of PAD treatment.	
Health Policy and Advocacy Improvement	Develop multidisciplinary teams of vascular specialists and nephrologists to create evidence based guidelines for management of PAD in CKD patients. Assure nephrology representation in all current amputation prevention clinical trials, health policy initiatives, and healthcare home initiatives. Create a “Call to Action” to utilize interdisciplinary health professional society leadership to foster creation of a national “PAD competent” workforce (PAD awareness would be provided to healthcare providers and patients). Such work is best initiated in concert with nephrology leadership.	

Prognosis

The mortality rate in people with PAD is approximately 50% at 5 years and 70% at 10 years[40]. Patients with PAD are at increased risk for all-cause mortality and from cardiovascular mortality[41]. Coronary heart disease is present in about 90% of people with severe PAD. The course of PAD is variable from gradual progression to more sudden deterioration. For people with intermittent claudication over a five-years period. Most people continue to have stable claudication.10-20% develop worsening symptoms .5-10% develop critical limb ischaemia. Amputation is eventually required in 1-2% but this increases to 5% in people with diabetes[40]. Critical limb ischaemia is also a marker for 13 eneralized, severe atherosclerosis, with a three-fold risk excess of future myocardial infarction, stroke, and vascular death compared with patients with intermittent claudication[42]. Critical limb ischaemia requires a major lower-limb amputation in about 30% of people within one year of diagnosis.Acute limb ischaemia has a poor prognosis, especially if diagnosis and treatment are delayed.Amputation may be necessary in up to 40% of people and the 30-days mortality can be up to 30%. Lower-limb artery bypass surgery is associated with up to 3% perioperative mortality and a mortality rate of almost 20% at one year.The prognosis following amputation is poor. Two years following a below-knee amputation, 30% are dead, 15% have an above-knee amputation, 15% have a contralateral amputation and only 40% have full mobility[42].

Prevalence in Bangladesh

Out of 100 paients 18 patients suffered from PAD, there was no age preponderance. Median age 50 yrs. 14 male and 4 female. Most (12 patients) patients in CKD stage V. 10 patients (56%) were asymptomatic. ABI score varies between 0.76 0.88. Distribution of risk factors among the PAD patients showing, among 18 patients 38.9% have DM, 72.2% have HTN, 33.3% have both DM & HTN, 44.4% have other vascular events, 55.6% are smokers, 33.3% have dyslipidemia & 22.2% have family history of PAD[43].

In a study on PAD in our country shows most of the patients were male (69 out of 89) patients[44].

The mean age was 54.49 ±18.36 yrs in male and 49.45 ±17.89 yrs for female in a study of NICVD on PAD[44]. Most of the patients of this series were more than 50 yrs of age (61.7%). In our contrast this male predominance may be due to lack of health checking behavior among the female.

Global prevalence

A predominance of the male gender with CKD is found in stages IV and V by Department of Nephrology and Neurology of University Hospital Virgen del Roc ´o, Seville, Spain in 2006[45]. Another study regarding the same topic shows 63.9% were male[46].

In a Kenyan study 35% pt is in 30-44 years range, 32% is in 45-59 year range and another 32% is above 59 years[47]. In the 2003–2006 NHANES study, the prevalence of CKD in people ages 60 was 24.5 percent. And in people between the ages of 20 and 39 was below 0.5 percent, that signifies the age related renal dysfunction[48]. Another study of NHANES on 2229 patients, a 24% PAD prevalence rate was observed in patients with estimated GFR <60 ml/min/1.73m^2 [49]. Another study including younger patients (55.7± 11.4 years) with a mean GFR of 30 ml/min has shown a prevalence rate of 22%[50].

In the Spanish study 30% of the PAD patients had intermittent claudication[51].

In another study,among the CKD patient who are positive for PAD 26% were diabetics, 10% active smokers, 48% ex-smokers, and 29% had a diagnosis of Coronary Heart Disease (CHD). 15% had been previously diagnosed of stroke, and 17% had signs and symptoms compatible with intermittent claudication[52].

A study done by Pakistan Institute of Medical Sciences shows twenty-five patients (34.7%) were in stage 3 CKD, 20 patients (27.8%) were in stage 4 CKD and 27 patients (37.5%) were in stage 5 CKD[46]. Another study had the study population with 2.1%, 16.5%, 34.5%, 22.2% and 24.7% in CKD stage 1,2,3,4 and 5 respectively[47].

Conclusions

Proportion of PAD among CKD patients is not low. Majority of the PAD patients had mild to moderate PAD and were in advanced CKD stage 4 – 5. There is need to actively look for PAD using ABI in patients with CKD without relying on symptoms as more than half are asymptomatic.Patients with diabetes, male gender and those with CKD stage 3 should have regular ABI measurement. Early aggressive management including risk factor modification should be done to improve outcome in this high-risk group by a multidisciplinary team approach including vascular medicine specialists, wound specialists, nephrologist and cardiologist. Further population-based studies are required to determine the proportion of PAD in the general population in our country.

Disclosure

All authors declare no competing interest.

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