



A Study on Carotid Intima-Media Thickness and Ankle Brachial Index In Patients with Various Stages of Chronic Kidney Disease

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ABSTRACT

The presence of peripheral vascular disease in chronic kidney disease portends a dismal prognosis due to the increased morbidity and mortality from cardiovascular events. Peripheral vascular disease is asymptomatic in about 40%. The study was designed to identify the prevalence of the peripheral vascular disease in chronic kidney disease, which is a state of accelerated atherosclerosis. A sample of 90 patients of chronic kidney disease attending the outpatient department in medicine and nephrology were assessed for the prevalence of peripheral vascular disease by measuring the Ankle-brachial index and Carotid intima-media thickness. Gender, smoking, hypertension, diabetes and ischemic heart disease profiles of the sample were analyzed for association with peripheral vascular disease. Majority of the patients belonged to the age group 40-50 years. 82 were males, of these 47 were smokers. 6 patients in the sample had symptoms suggestive of peripheral vascular disease. While 21%(n=19) of patients in the sample were diabetics and 21%(n=19) had evidence of ischemic heart disease, hypertension was present in 41%(n=37) of the patients. 50% of the patients belonged to CRF stage 4. The prevalence of the peripheral vascular disease, as determined by ABI<0.9, was 31.1%. CIMT thickness > 0.9mm has a positive correlation with CKD stages and has a statistically significant P value of <0.05. In conclusion, this study revealed that there is an increased prevalence of PVD in smokers, diabetics and in ischemic heart disease compared to those with hypertension.



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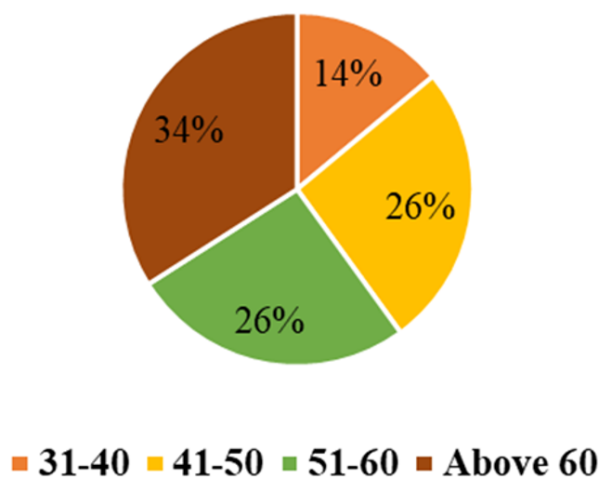
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INTRODUCTION

The global burden of chronic kidney disease (CKD) has been increasing in recent times. As the morbidity and mortality from communicable diseases decline, life expectancy increases and degenerative diseases have become more common (Patel *et al.*, 2019). CKD is amongst the chronic-non-infectious illnesses in that there is a very real opportunity to continue living comfortably in spite of being terminally ill (Enas *et al.*, 2008). A survey in the United States have estimated that 6% of the population has chronic kidney disease at stages 1 and 2 and 4.5% had stages 3 and 4 CKD (Lawal *et al.*, 2019).

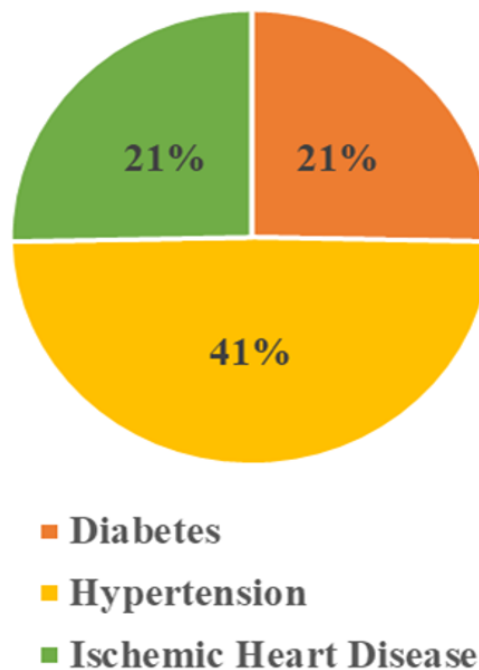
National Health and Nutrition Examination Survey (NHANES) data had shown that PAD prevalence was higher (14.5%) in 70 years age group and 2.5% in the 50 to 59 years group (Polak *et al.*, 2019). There is a twofold increase risk of developing Peripheral Artery Disease in patients with compromised renal function. The NHANES revealed that 24% belonging to the 40 years age group had creatinine clearance < 60ml/min per 1.73 m² to have an Ankle-brachial index < 0.9. Compared to the Western population prevalence of PVD in Indians is relatively low. In diabetic patients from south India, there was 3.9% of PVD (Mohan *et al.*, 1995). There is an increase in PVD in diabetics with age, below 50 years, it was 3.2% and in those above 80 years, it was 33% (Patel *et al.*, 2019). Increases in the duration of diabetes also increased the prevalence of PVD from 15% to 45% at 10 to 20 years after diabetes diagnosis (Patel *et al.*, 2019). Patients above 80 years with diabetes for more than 30 years are extremely low; this relates to the low prevalence in India (Kuswardhani *et al.*, 2018).



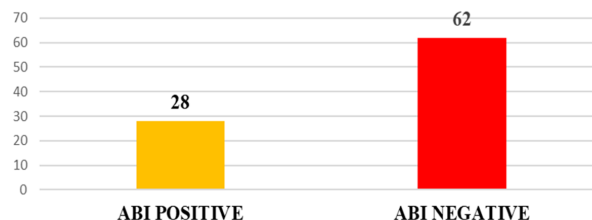
Graph 1: Age distribution

Type 2 Diabetes mellitus leading to diabetes nephropathy stands to be the major cause for Chronic Kidney Disease (Longo *et al.*, 2012). India, being the Diabetic capital of the world and diabetic nephropathy being the commonest cause of CKD, the prevalence of PVD is on the rise. There are about 7.85 million CKD patients in India (Dash and Agarwal, 2006). Chronic kidney patients are at high risk for developing cardiovascular diseases. In patients with CKD, the risk of cardiovascular disease was 10-20 folds more compared to the general population (Longo *et al.*, 2012).

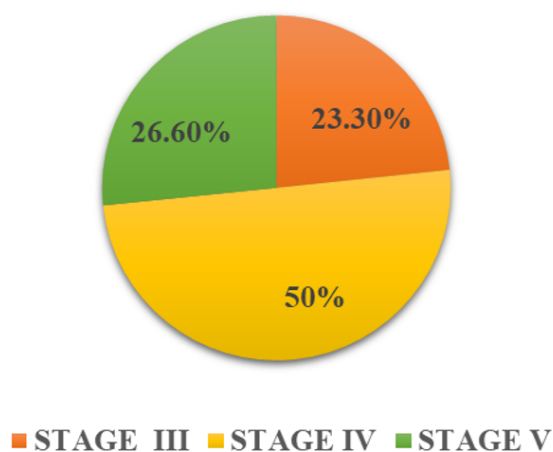
Measuring the carotid intima-media thickness by ultrasonography in patients with chronic kidney disease is a relatively simple, non-invasive method of



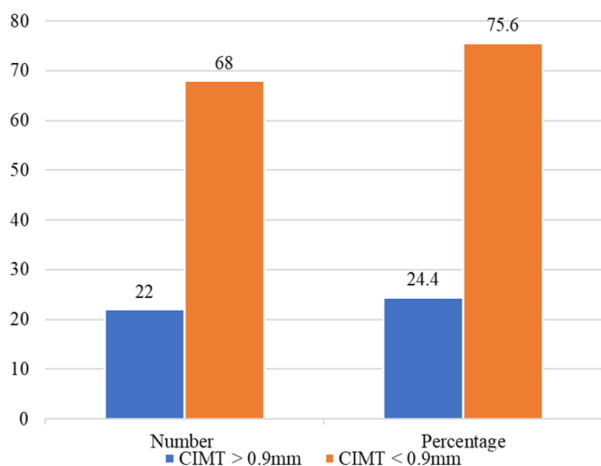
Graph 2: Prevalence of risk factors in the study population



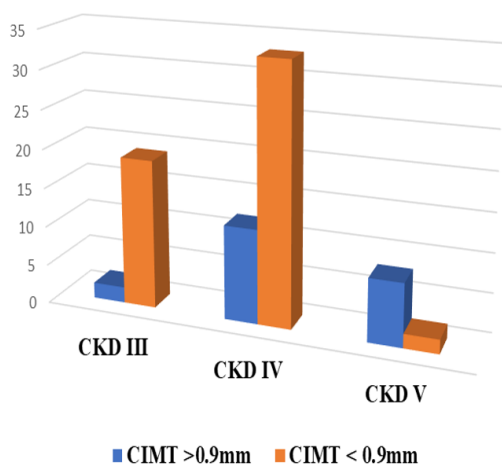
Graph 3: Correlation between ABI and the prevalence of the peripheral vascular disease



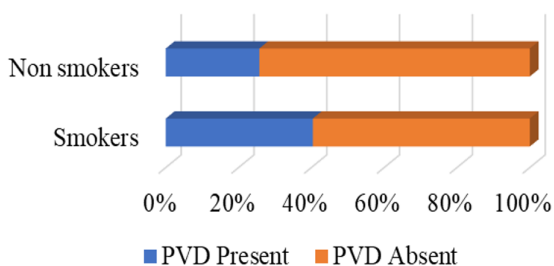
Graph 4: Stages of CKD



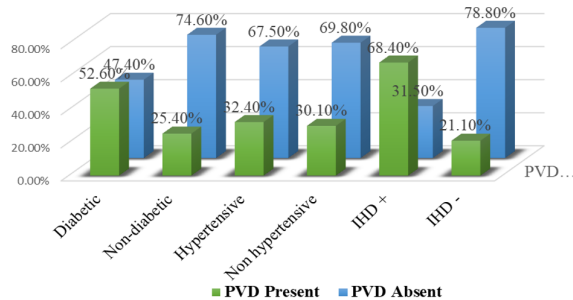
Graph 5: Number of CKD patients with CIMT >0.9mm



Graph 6: Correlation between CKD stages and CIMT



Graph 7: Correlation between smoking and prevalence of the peripheral vascular disease



Graph 8: Correction between risk factors and PVD

assessing atherosclerosis. CKD patients are vulnerable to develop cardiovascular and cerebrovascular complications. CIMT measurements assess the risk for future cardiovascular events and analyze the effect of drug therapy (Guerrero *et al.*, 2006). Increased incidence of Peripheral vascular disease in CKD is due to atherosclerosis. While at most attention is given to the detection of coronary artery disease in CKD patients, the high mortality rate in PAD is not examined in these patients. This is not only due to the lack of awareness of the remarkably high prevalence of PAD among CKD patients but to the asymptomatic nature of the disease, fewer than 50% of patients with PAD are symptomatic, thus defining a population with subclinical PAD (Longo *et al.*, 2012).

Rise in the number of patients with clinical and sub-clinical peripheral vascular disease in chronic kidney disease has led to the need of screening all patients with CKD for PVD. A riskless, cost-effective, non-invasive approach to screen all patients with CKD for PAD is necessary (Kuswardhani *et al.*, 2018). The resting ABI (Ankle Brachial Index) is a sensitive and specific screening test used for establishing the diagnosis of PAD (CDC, 1999). People with asymptomatic PAD should be identified and appropriate interventions should be done to reduce their increased risk of myocardial infarction, stroke, and death (Sonoda *et al.*, 2019). This study is designed to determine the prevalence of PAD affecting the lower limbs in a population of CKD patients using the Ankle-Brachial index and also by measuring carotid intima-media thickness, which is cost-effective and non-invasive since CKD patients are more susceptible to develop complications resulting from accelerated atherosclerosis.

MATERIALS AND METHODS

This cross-sectional study included patients attending or admitted in the department of medicine or nephrology in Saveetha medical college hos-

pital during the period of February 2016 – April 2017. Inclusion criteria were patients of chronic kidney disease with a creatinine clearance of <90ml/min/1.73m (stages 2,3,4,5), exclusion criteria were patients with an established diagnosis of peripheral arterial disease, patients on Dialysis.

The ethical committee of the institution approved the study. A well designed proforma was used to obtain the demographic and clinical details of the patients. Sample of 90 continuous patients who met the inclusion criteria were recruited in the study. Informed consent was obtained from all the participants. The modified kinetic Jaffe method was used to measure serum creatinine. Since age, ethnicity and gender influences the levels of serum creatinine, the level of renal function was confirmed by eGFR by Modification of Diet in Renal Disease (MDRD). The MDRD formula is as follows: $eGFR = 186.3 \times (\text{serum creatinine}^{-1.154}) \times (\text{age}^{-0.203}) \times 1.212$ (if black) $\times 0.742$ (if female). In individuals without prevalent PAD, the ABI was determined. The ABI was obtained using the ABI TONOMETER in the Department of Vascular Surgery. Posterior tibial, pedal arteries and the brachial artery was used to measure the Systolic Blood Pressure (SBP). Ankle Brachial Index (ABI) was determined by dividing the greater SBP (lower limbs) the SBP of the upper limbs. The lowest ABI so used in the statistical analyses. A value of ABI <0.9 was considered pathologically low.

A master chart was created and the statistical analysis was done using Epidemiological Information Package (EPI 2002) software. Mean, SD, percentage, frequencies and range are calculated. Kruskal Wallis test, chi-square test was used for quantitative variables and Yates's test for qualitative variables. A 'p' value less than 0.05 was considered to be statistically significant.

RESULTS AND DISCUSSION

In this cross-sectional study, a total of 90 patients were included of which 91%(n=82) were male and 8%(n=8) were female. While studies by [de Vinuesa et al. \(2005\)](#); [Guerrero et al. \(2006\)](#) showed an increased prevalence of the peripheral vascular disease in males ([Guerrero et al., 2006](#); [de Vinuesa et al., 2005](#)). [Mostaza et al. \(2006\)](#) found increased prevalence in females. The HEMO study also does not find a significant statistical association between male sex and the prevalence of PAD in patients with ESRD [Mostaza et al. \(2006\)](#). Graph 1 shows the age distribution among the study population, the majority of the patients belonged to the age group 40-50 years and 47 males were smokers.

Six patients in the sample had symptoms suggestive of peripheral vascular disease. This is in agreement with the study ([Suominen et al., 2008](#)) in Finland, wherein the prevalence of PAD was significantly more among subjects with severe symptoms (rest pain, ulcers or gangrene), accounting for about 83.8%. Graph 2 shows the percentage of risk factors in the included patients, of which 50% of the patients belonged to CRF stage 4.

Graph 3 shows the prevalence of peripheral vascular disease as determined by ABI<0.9 was 31.1%. Studies by [Guerrero et al. \(2006\)](#); [de Vinuesa et al. \(2005\)](#) and [Herath et al. \(2019\)](#) in which the prevalence of PAD was 24%, 19%, 32% and 29% respectively ([Guerrero et al., 2006](#); [de Vinuesa et al., 2005](#); [Herath et al., 2019](#)).

Among the variables studied, smoking (p=0.047), diabetes (p=0.023), presence of IHD (p=0.001) and creatinine clearance (p=0.047) were identified as having a significant association with increased prevalence of PAD. All symptomatic patients had peripheral vascular disease (ABI<0.9) but of the asymptomatic patients, 26.1 % (n=22) had evidence of PAD. Graph 4 shows the various stages of CKD in the included 90 patients. The studies by ([Chen et al., 2009](#); [Stenvinkel et al., 1999](#)) showed a fivefold increase in the risk of PAD among patients with a history of smoking. The HEMO study found that smoking was associated with the peripheral vascular disease among haemodialysis patients. In the MERITO study, the prevalence of smoking in patients with CKD was 11.1% ([Mostaza et al., 2006](#)). In a study by [Herath et al. \(2019\)](#) there was no difference in pack-years of smoking between subjects with GFR above or below 60ml/min/1.73m ([Herath et al., 2019](#)).

There was an inverse correlation between creatinine clearance and the prevalence of PVD. Of the 90 patients in the study group, 45 patients had stage 4 CKD. In stage 3, CKD patients with ABI<0.9 PAD was 14% in patients and 35% in stage 4 and 37.5% in stage 5. The higher the stages of CKD, the higher the prevalence of PVD. Graph 5 shows the number of CKD with CIMT, CIMT thickness > 0.9mm CIMT has a positive correlation with CKD stages and has a statistically significant P value of <0.05. In the ARIC study the prevalence of atherosclerosis with increasing severity of the renal failure. ([Abramson et al., 2003](#)). Graph 6 shows the correlation between CIMT and stages of CKD, of the 21 patients belonging to stage 3 CKD, 2 patients had CIMT thickness >0.9mm and 12 patients had CIMT thickness>0.9mm out of 45 patients belonging to stage 4 and 8 patients out of 24 patients belonging to stage

5 had CIMT thickness > 0.9mm CIMT has a positive correlation with CKD stages and has a statistically significant P value of <0.05. Carotid intima-media thickness can be considered as an alternative marker of atherosclerosis. CIMT is a non-invasive and easy diagnostic test and it is cost-effective in patients with chronic renal failure (Lawal *et al.*, 2019). CIMT measurement was first described by Lawal *et al.* (2019) was used to detect atherosclerosis, a progression of the disease and prognosis of treatment. Lawal *et al.* (2019). A study by (Weatherley *et al.*, 2006) revealed that arterial changes was due to dyslipidaemia in renal disease progression. A study by Patel *et al.* reported that patients belonging to stage 3 and 4 had a significant increase in CIMT values (Patel *et al.*, 2019). Ji-Cheng and Zhang (2019) in their study on CKD stages between 2 to 3 found significantly increased values of CIMT and they concluded that arterial changes can occur even in early stages of CKD (Ji-Cheng and Zhang, 2019).

Peripheral vascular disease was present in 29.3% of males (n=24) and 50% of females (n=4). Applying a chi-square test, the difference did not show statistical significance (p=0.229). Of the 90 patients of CKD, 23 patients had dyslipidaemia. Graph 7 shows a correlation between smoking and the prevalence of the peripheral vascular disease. Smokers had significantly increased risk of having low ABI compared with non-smokers. ABI was less than 0.9 in 40.4% of smokers (n=19), whereas it was 25.7% among non-smokers (n=9). Chi-square test with Yates correction showed a p<0.05. There was a positive correlation between smoking and the prevalence of the peripheral vascular disease. The studies have shown a fivefold increase in the risk of PAD among patients with a history of smoking (Suominen *et al.*, 2008). The HEMO study found that smoking was associated with the peripheral vascular disease among haemodialysis patients. The variation in this study could be due to the lesser number of active smokers in the group; only 10% of the 58% of smokers were active smokers, the rest 48% were ex-smokers.

The number of patients with diabetes having Peripheral vascular disease was 10, which accounted to 52.6%. Applying a chi-square test, the difference showed a statistical significance (p<0.05). Of the non-diabetic patients, 25.4% developed the peripheral vascular disease. Graph 8 shows the correlation between various risk factors and PVD. A study done in India showed that the prevalence of PAD in diabetic patients be about 3.9%. (Pendsey, 1998) However, this varies with the duration of diabetes as brought about by Mohan *et al.* (1995) wherein the prevalence of PAD in

diabetics was 2% at diagnosis and 4% at 10 years duration and 8% at 20 years duration (Mohan *et al.*, 1995). 37 patients had hypertension in the study group. Abnormal ABI was present in 32.4% of the hypertensive patients, whereas abnormal ABI was seen in 30.1%, which had no statistical significance. The Data obtained in the MERITO study patients with no history of cardiovascular disease have shown a GFR <60 ml/min per 1.73 m² with albuminuria, but had low ABI (Mostaza *et al.*, 2006). 25% of patients with decreased GFR or albuminuria had reduced ABI. There was 50% increase in patients with both disorders. The incidence of PAD in the hypertensive population in the ARIC study was 43% (Suominen *et al.*, 2008). 19 patients in the study group had coronary artery disease. The analysis showed that, of patients with ischemic heart disease, 13 (68.4%) had peripheral vascular disease, whereas 21.1% of patients without IHD had peripheral vascular disease. Three similar studies had strong association has been found between the presence of CAD and peripheral vascular disease in patients with CKD. The difference was found to be of the 90 patients screened, all the patients (n=6) who were symptomatic had a peripheral vascular disease and 26.1% who were asymptomatic had peripheral vascular disease. The difference was significant, as determined by the chi-square test. The prevalence of the asymptomatic peripheral vascular disease in CKD patients in the present study is 26.14%.

The limitations in this study are Ankle-brachial index is used as the absolute criterion for diagnosing peripheral vascular disease in our study. The ankle-brachial index is 95% sensitive and 99% specific for peripheral vascular disease; false positive and false negative results are possible rarely. False-positive results could be ruled out by following up all abnormal ABI with the Duplex ultrasonography probe, which was not done in our study. The number of false-negative results could be decreased further by doing the exercise ABI, which was not done in our study. False positives can be seen in diabetes mellitus and renal failure because of non-compressible and calcified lower extremity arteries. This would result in spuriously high ABI values. Further, in these patients with non-compressible vessels, a toe brachial index (TBI) can be measured using a small toe cuff and PPG (Photoplethysmography), which was not done in our study. The patients in our study comprised mainly of those in Stage 4 or 5 and many were on intermittent dialysis. The ankle-brachial index in patients on dialysis and in non-dialyzed patients varies to a considerable extent. This factor was not taken into account in our study.

CONCLUSION

The prevalence of the peripheral vascular disease in patients with Chronic Kidney Disease was 31.1%. There was a significant relationship between the prevalence of peripheral vascular disease and the stage of chronic kidney disease; the higher the degree of renal insufficiency, the higher was the prevalence of the peripheral vascular disease. The prevalence of the peripheral vascular disease in chronic kidney disease was increased in smokers, diabetics and in patients with ischemic heart disease. Gender and Hypertension were not associated with an increased prevalence of the peripheral vascular disease in patients with chronic kidney disease. There was a significant relationship between the prevalence of chronic kidney disease and carotid intima-media thickness. The higher the degree of renal insufficiency, the higher was the carotid intima-media thickness. Measuring the CIMT using ultrasound Doppler is an effective non-invasive method in assessing atherosclerosis. Hence it is concluded that smoking cessation, control of diabetes and adequate treatment of ischemic heart disease will lower the incidence of PVD in patients with CKD, which may be very beneficial in controlling further decline of renal function and hence improving the morbidity and mortality.

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Conflict of Interest

None.

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