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# Relationship Between Femoral Artery Intima-Media Thickness And Atherosclerosis In Patients With Chronic Kidney Disease- A One Year Hospital-Based Cross-Sectional Study

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# Relationship Between Femoral Artery Intima-Media Thickness And Atherosclerosis In Patients With Chronic Kidney Disease- A One Year Hospital-Based Cross-Sectional Study

#### Abstract

**Introduction**: Chronic kidney disease (CKD) is one of the leading causes of morbidity and mortality worldwide. CKD and Peripheral arterial disease both independently increase the risk for cardiovascular disease (CVD) events and contribute significantly to morbidity and mortality. There is limited data about the co-relation between ultrasound measures of the femoral artery in peripheral vascular disease (PVD) & renal functional status. This research hence will help us in the establishment of a relationship between femoral intima-media thickness (fIMT) with CKD. Also, IMT assessment might help in earlier detection of atherosclerotic plaques & hence PVD.

**Materials and methods:** A cross sectional study was conducted for 1 year in a tertiary care hospital. 99 CKD patients with no history of smoking & hypertension were enrolled, who underwent femoral Doppler ultrasonography. The findings of ultrasonography were analysed. Descriptive analysis was carried out for the quantitative data.

Results: The mean age was 52.42 ±15.95 years, mean femoral intima media thickness (fIMT) was 0.08±

0.02cm and mean estimated glomerular filtration rate (eGFR) was 17.44±15.44ml/min/1.73m<sup>2</sup>. In this study men were more commonly affected, most vulnerable age being >60 years. Out of 99 subjects, 69 had raised IMT and 30 patients had normal IMT. Prevalence of atherosclerosis in the given study group was found to be 69.70 %. Higher prevalence of raised IMT among diabetics (75.0%) was present. Not all CKD groups had significant co-relation with IMT.

**Conclusion**: Prevalence of atherosclerosis was high in CKD population, more common in men and in the older age group. None of the CKD Stages had any significant co-relation with PVD. Femoral artery plaques identified by ultrasound are independently associated with lower eGFR. Femoral artery doppler ultrasonography will be a promising tool for identifying atherosclerosis in kidney disease in its earlier course.

#### Keywords

Atherosclerosis, chronic kidney disease, ultrasonography, peripheral vascular disease, plaque, intima media thickness.

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#### Introduction

Chronic kidney disease is one of the leading causes of morbidity and mortality worldwide. Exact prevalence of chronic renal disorder is not known in Indian subcontinent since not many longitudinal studies have been done. As per a few studies, however, it is estimated approximately to be 800 /million population.<sup>1</sup> Atherosclerosis is a major mortality factor in India, commonly noticed with chronic kidney disease (CKD) patients. CKD-related metabolic abnormalities, endocrine abnormalities, and inflammatory conditions have also been known to play a role in atherosclerosis in cardiac disorder patients<sup>2</sup> Chronic kidney disease (CKD) is associated with peripheral artery disease (PAD)<sup>3</sup>.CKD and Peripheral arterial disease both independently increase the risk for cardiovascular disease (CVD) events and contribute significantly to morbidity and mortality.<sup>4-6</sup> For more than 40 years ankle brachial index (ABI) has been used for peripheral arterial disease<sup>7</sup>, however, this index is considered less sensitive in the early stage of PAD, where there is earlier development of atherosclerosis and vessel dysfunction than a lower ABI since it needs a plaque that's sufficiently occlusive enough to decrease blood pressure distally. Also using ABI in CKD patients is troublesome as there is a higher chance of them having stiff arteries, leading to a lower sensitivity of ABI.<sup>8-10</sup> Many studies have shown that there is an association between increased carotid Intima Media Thickness (cIMT)<sup>11-12</sup> and decreased kidney function, in fact, it has been proved many times that there is a faster increase in cIMT.<sup>13</sup>However, in contrast to carotid atherosclerosis, femoral atherosclerosis has been less studied. Some studies have shown that subclinical atherosclerosis is most likely identified in femoral arteries than carotid arteries (54% vs34%)<sup>14,15</sup>. Hsu et al found that CKD was quantifiably having association in relation to plaque prevalence of femoral artery, even in subjects with normal ABI.<sup>16</sup>

There is limited data about the co-relation between USG measures of the femoral artery of peripheral vascular disease & renal functional status. Hence This study was done to study the relationship between femoral artery intima-media thickness and atherosclerosis in patients with chronic kidney disease using femoral Doppler ultrasonography. IMT assessment might help in earlier detection of atherosclerotic plaques & hence podcast-effectiveness, patient ease, reduced radiation risk has made femoral Doppler ultrasonography a preliminary investigation in assessing peripheral vessels.

### Objectives

- To assess the femoral vessel IMT in CKD subjects.
- To calculate the estimated eGFR in CKD patients & analyse the relationship of femoral IMT in subjects with low eGFR

### Materials and methods

The study was a hospital-based cross-sectional study carried out on 99 patients between January 2020 – December 2020 who were known cases of CKD patients referred from department of nephrology to the radiology department of KLE'S Dr. Prabhakar Kore Hospital Belagavi for femoral Doppler ultrasonography. As stated by the kidney International Journal, CKD is defined as when the GFR is less than 60 ml per min per 1.73 m<sup>2</sup> for more than 3 months, irrespective of cause. <sup>17</sup> Exclusion criteria were

- Patients diagnosed with type I diabetes mellitus or hypertension or with history of smoking which are also risk factors for atherosclerosis.
- Patients who underwent surgical / interventional treatment of carotid arteries for atherosclerotic disease.
- Patients diagnosed with gestational diabetes mellitus.
- Patients with past renal transplant
- Patients with a known case of renal malignancy based on their history and medical records.
- Patients who underwent surgical/interventional treatment of femoral arteries for atherosclerotic disease.

This research was accepted by an institutional human ethics committee (MDC/DOME/292). An informed written consent was received from all the subjects. A pre-structured proforma was used to gather baseline demographic and clinical data. Using the demographic data and creatinine values, the GFR was estimated using the recent CKD EPI formula<sup>18</sup>.

The CKD EPI equation being:

GFR = 141 x min (S. creatinine / $\kappa$ , 1)<sup> $\alpha$ </sup> x max (S. creatinine / $\kappa$ , 1)<sup>-1.209</sup> x 0.993<sup>Age</sup> x 1.018[for female] x 1.159 [for African]

 $\kappa$  = 0.7 in female and 0.9 in male,

 $\alpha$  = -0.329 in females and -0.411 for male.

#### Ultra sound protocol and vascular measurement

The study population was subjected to femoral artery Doppler ultrasonography on GE VOLUSON machine (GE Healthcare, USA) fitted with a linear array transducer of 7.5-12 MHz high frequency.

Patients were positioned supine with their legs extended. The examination was started with a transverse scan of the left and right thigh regions. Scanning was performed in the following areas: right and left femoral area. The CFA & SFA would be focused, & IMT would be measured on the transverse axis.

High-resolution ultrasonography is used to visualize various strata of arterial walls. In the long axis, the two walls appear as hyperechoic lines with a dark region in between. The initial echoic line on the farther wall originates from close opposition between vascular lumen, while later nearer echoic line originates from apposition between medial & adventitial layer. The inside margin of an echoic adventitial layer is sharpened by a less bright medial layer. Combined intima-media thickness is the length between the distance from the first bright line along the far wall to the second bright line.

Plaque: It is defined as a focal structure that encroaches into the arterial lumen of at least 0.5 mm or 50% of the surrounding IMT value or demonstrates a thickness >1.5 mm as measured from the media-adventitia interface to the intima-lumen interface. Plaques were detected by B-mode ultrasonography, value  $\geq$ 1.2 mm (lumen to adventitia) indicated the presence of plaque.<sup>19</sup>

#### **Statistical Analysis:**

In the present cross-sectional analysis, the mean and standard deviation were determined for the continuous quantitative variables. For comparative purposes, the continuous variables were compared using appropriate methods, such as ANOVA, correlation, regression, etc. Discrete variables were represented by a median. The relation between the result, clinical and demographic characteristics were evaluated using either the Chi-square or the exact Fisher test. The value of p less than 5% (0.05) will be considered important for all the tests.

#### Results

Total ninety-nine CKD cases were prospectively studies in this study. The study had most of the subjects from age of 51-60 years (26.26%), trailed by 61–70-year (23.23%) age group. The mean age was (52.39 $\pm$  15.89) years. In the current study percentage of male patients were more (70.71%) as compared to the female patients (29.29%). Out of 99 CKD patients ,46(46.46%) had a symptom of oedema, 28(28.28%) had symptoms of decreased urine output ,15 (15.15%) had blackish discoloration of foot and 10(10.10%) had urticaria. The study had borderline high percentage of non-diabetics, the percentage being 51.52%, whereas diabetics in study constituted 48.48% (Figure 1 or Table 1). Maximum number (61) of patients had eGFR values < 15 mL per min per 1.73m<sup>2</sup>. 4 patients had eGFR values between 60-90 mL per min per 1.73m<sup>2</sup> range. Majority of patients were in stage 5(61.62%) followed by stage 4(22.22%), stage3B (8.08%), stage 2(4%) and stage 3A (4%) (Figure 2 or Table 2).

In the current research, 69 cases (69.70 %) had raised IMT and 30 (30.30%) cases did not have any atherosclerotic changes, suggesting a significant prevalence of atherosclerosis. Maximum numbers of cases with raised IMT were in the age

group of 61-70 years, however all the subjects of age group of 71 to 80 years had raised IMT, making it the vulnerable age group (Figure 3 or Table 3). Majority of patients (92) had creatinine in the range of 1.3-10 mg/dl, 6 patients had in the 11-21mg/dl range and just one patient had creatinine >21mg/dl.

In the present study it showed that out of the 48 diabetic patients, 36 diabetic patients (75.0%) had raised IMT though statistically not significant (p= 0.1190).31 patients out of 69 patients with raised IMT had femoral wall thickness, but it was statistically not significant(p=0.6) (Figure 4 or Table 4). Out of 99 subjects 20 patients had peripheral vascular disease. The study showed that all the patients with eGFR range 30-44 mL/min/1.73m<sup>2</sup> had raised IMT and most of the patients (86.36%) with eGFR range 15-29 mL/min/1.73m<sup>2</sup> had raised IMT. (Figure 5 or Table 5). The study showed that patients with eGFR range 15-29 mL/min/1.73m<sup>2</sup> had raised IMT. (Figure 6 or Table 5). The study showed that patients with eGFR range 15-29 (mL/min/1.73m<sup>2</sup>) had maximum triglyceride levels which is statistically significant (Figure 6 or Table 6). The present study showed that, about 91.92 % of the CKD subjects were anaemic and 16.16% subjects undergoing haemodialysis treatment.

#### Discussion

Chronic kidney disease is a stand-alone threat for atherosclerosis. Atherosclerosis is a gradually progressing disease over several decades before signs and symptoms. It would be too late by the time complications arise as it's a silent disease and would have already caused irreversible histological alterations Colour Doppler ultrasonography is a non-invasive and cost-effective imaging modality that has a vital function in assessing the severity of atherosclerosis and PVD in CKD patients. The current study included 99 patients; among them male patients (70.71%) were more than female (29.29%) patients. The maximum number (19) of subjects who had raised IMT were from the age group of 61-70 years. However, all the patients of age group 71-80 years had raised IMT, making this age group the most vulnerable age for atherosclerosis. Men were more affected as compared to women. Research by Simon Hsu et al. showed that the prevalence of plaque was higher in males, which is consistent with our study.<sup>16</sup>

In this study out of 99 patients, 69 patients (69.70%) had raised IMT, whereas 30 patients (30.30%) did not have raised IMT without evidence of any atherosclerotic plaques, making the prevalence of atherosclerosis in the given CKD population as 69.70%. This was in consistency with a research of Nariman et al, who had higher femoral IMT in chronic kidney disease subjects in comparison with normal individuals.<sup>20</sup>The result was also matching with a study by Simon et al., who had a plaque prevalence of 46% among 156 CKD patients .In another observational study conducted by Gracia et al on 1553 CKD patients who underwent USG carotid and femoral found that high prevalence of atherosclerosis (68.9%) and also found that plaque progression was associated with concurrent CKD progression<sup>21</sup>.

Though the prevalence of atherosclerosis in the CKD population was high (69.70%), the percentage of subjects having peripheral vascular disease was 20.20 %, which is similar to the study by Ohare et al where the prevalence of PAD in renal insufficiency was found to 24%<sup>3</sup>. The prevalence of PVD in other studies ranges from 24% to 37% which is consistent with the present study.<sup>22,23</sup> ARIC study by Wattanakit et al concluded that incidence of PAD was 8.6per 1000per year in CKD patients with RR of 1.56(95%CI 1.13 to 2.14)<sup>24</sup>

In the present study out of 99 subjects, 48(48.48%) subjects had diabetes. Of the 48 diabetic patients, 36 diabetic patients (75.0%) had raised IMT, suggesting a high prevalence of atherosclerosis among diabetics. The study by Le et al also had similar results wherein femoral artery was thickened in 38.2 % of diabetics.<sup>25</sup>in a study conducted by Palance et al on 1548 CKD patients ,419 patients were diabetic constituting 27%. The frequency of femoral plaques at any site (with or without the presence of carotid plaques) was significantly higher in DM patients (58.5% vs. 47.5%, p < 0.001). However, no significant differences were found in the percentage of patients with femoral plaques but without carotid plaques. The proportion of patients with atherosclerotic plaques in both sites, carotid and femoral, was also higher in DM patients (46.1% vs. 34.2%, p < 0.001). The prevalence of patients presenting plaques at either the carotid or the femoral site was significantly higher among patients with DM (81.4% vs. 64.1%, p < 0.001).<sup>26</sup>

In our study only groups with eGFR values 15-29 & 30-44 mL/min/1.73m<sup>2</sup> had a strong positive correlation fIMT. This is in contradiction to the study by Hsu et al, who had a significant association with lower eGFR values and higher fIMT values<sup>16</sup>. However, the adjusted model in terms of age, sex, race, the association was no longer was significant. Similar results were obtained as stated above since CKD categorization into stages depends on the eGFR values. Our study showed that only CKD Stages 4 & 5 had more prevalence of higher IMT.

According to the presents study results, 13.11 % of patients with eGFR < 15 mL/min/1.73m<sup>2</sup> had PVD ,36.36 % of patients with eGFR range 15-29 mL/min/1.73m<sup>2</sup> had PVD, 25% of the patients with eGFR range 30-44 , 45-59 & 60-90 mL/min/1.73m<sup>2</sup> had PVD .(p = 0.22) This suggests that none of the eGFR patients groups had any significant co-relation with PVD.

NEFRONA study showed a clear trend towards higher prevalence of plaques with more advanced CKD categories, confirming that severity of CKD is an independent factor influencing subclinical atheromatosis (odds ratio [OR] G3: 1.29; 95% CI, 0.99–1.67; P=0.058; OR G4: 1.72; 95% CI, 1.32–2.24; P=0.001; OR G5: 3.74; 95% CI, 2.80–4.98; P<0.001 versus control patients.<sup>27-29</sup>.

Accordingly, none of the CKD Stages had any significant co-relation with PVD.

In the present study, the patients with eGFR range 15-29 (mL/min/1.73m2) had maximum triglyceride levels which is statistically significant. similar to the present study, other study conducted by Wang Y et al found that serum triglyceride level showed a negative correlation with measured GFR (mGFR) ( $\beta$  = -0.006, *P* = 0.006) in linear regression analysis and concluded that serum triglyceride level is independently association with mGFR. Patients with reduced kidney function are more likely to have higher serum triglyceride levels<sup>30</sup>.

#### Limitation

As the present study is a cross sectional study, precludes determination of whether femoral artery measures of PAD precede CKD or vice versa. The study includes small sample size which may again be a limitation and needs further studies with larger sample size. Future studies should also assess for associations between femoral ultrasound vascular measures and change in eGFR over time and whether femoral artery ultrasound might identify prevalent PAD. Such studies may ultimately allow early detection of PAD and hence prevention of complications associated such as lower limb infections and amputations.

## CONCLUSION:

Prevalence of atherosclerosis was high in CKD population, more common in men and in the older age group. None of the CKD Stages had any significant co-relation with PVD. Femoral artery plaques identified by ultrasound are independently associated with lower eGFR. Femoral artery ultrasound will be a promising tool for identifying atherosclerosis in kidney disease in its earlier course.

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### **Conflict of interest**

None

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Figure or Tables:

Figure	1 or Table <sup>·</sup>	1. Demographic	features and	d clinical	characteristics

1	Age (in years) distribution	
	≤30	10(10.10%)
	31-40	13 (13.13%)
	41-50	19 (19.19%)
	51-60	26(26.26%)
	61-70	23(23.23%)
	71-80	8(8.08%)
2	Mean age (in years)	52.39 ± 15.89
3	Gender	
	Male	70 (70.71%)
	Female	29(29.29%)
4	Symptoms	
	edema	46(46.46%)
	Urticaria	10(10.10%)
	Foot black discoloration	15(15.15%)
	Decreased urine output	28(28.28%)
5	Diabetes Mellitus	
	Yes	48(48.48%)
	No	51(51.52%)
Figure 1	or Table 1. Demographic features a	and clinical characteristics
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Figure 2 or Table 2: Descriptive analysis of distribution in terms of CKD stages (N=99

Figure 3 or Table 3: **Descriptive analysis of distribution in terms of prevalence** of raised IMT among different age groups (N=99).

Age groups	Raised IMT	Not raised IMT	P value	
	N(%)	N(%)		
<=30yrs	6(60.00%)	4(40.00%)	p=0.0070, S	
31-40yrs	8(61.54%) 5(38.46%)			
41-50yrs	10(52.63%)	9(47.37%)		
51-60yrs	18(69.23%)	8(30.77%)		
61-70yrs	19(82.61%)	4(17.39%)		
71-80yrs	8(100%)	0		
Total	69(69.70%)	30(30.30%)		

# Figure 4 or Table 4: Descriptive analysis of association of DM and femoral wall

# thickness with raised IMT

	Raised IMT	Not raised IMT	P value
Diabetes mellitus			
Present	36(75.00%)	12(25.00%)	p=0.1190
Absent	33(64.71%)	18(35.29%)	-
Femoral wall			
thickness	31(86.11%)	5(13.89%)	p=0.6090
Present	38(60.32%)	25(39.68%)	
Absent	. ,	. ,	

Figure 5 or Table 5: Descriptive analysis of association between eGFR and IMT

# (N=99).

eGFR(mL/min/1.73m <sup>2</sup> )	Raised	Not raised	Total	
	%	%	%	
60-90	2(50%)	2(50%)	4(4.04%)	
45-59	5(62.50%)	3(37.50%)	8(8.08%)	
30-44	4(100%)	0	4(4.04%)	
15-29	19(86.36%)	3(13.64%)	22(22.22%)	
<15	39(63.93%)	22(36.07%)	61(61.62%)	
Total	69(69.70%)	30(30.30%)	99(100%).	
Chi-square=6.5232, P = 0.1630				

# Figure 6 or Table 6: Descriptive analysis of association between eGFR and TG

(N=99).

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eGFR(mL/min/1.73m <sup>2</sup> )	100-200mg/dl	201-	%	>301mg/dl	%
	(%)	300mg/dl			
60-90	1(25%)	3	75.00	0	0.00
45-59	2(25%)	1	12.50	5	62.50
30-44	0	10	45.45	12	54.55
15-29	2(3.28%)	25	40.98	34	55.74
<15	0	4	100.0	0	0.00
Total	5(5.05%)	43	43.43	51	51.52
Chi-square= 21.4390, P = 0.0060, S					