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Carotid Artery Disease in Patients with Chronic Kidney Disease

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Abstract

Objective: *1. To study the prevalence of carotid artery disease in patients with chronic kidney disease using carotid artery intima media thickness as a surrogate marker, measured by B mode ultrasonography. 2. To study the co relation of carotid intima media thickness with glomerular filtration rate and other cardiovascular risk factors*

Background: *The present study is aimed at studying the prevalence of atherosclerosis in patients with CKD using carotid intima media thickness (CIMT) as a surrogate marker of atherosclerosis and co relating the various CVD risk factors and declining renal function in the causation of atherosclerosis.*

Materials And Methods: *Seventy patients with CKD, defined by NKF/KDOQI guidelines, attending nephrology OPD were studied for demographic data and CIMT values and comparing with thirty age and sex matched controls. CIMT was derived via B-mode ultrasonography and CKD was evaluated by the estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease Study equation.*

Results: *Mean CIMT in CKD patients was 0.86± 0.21 mm and that in healthy age and sex matched controls was 0.63±0.17mm which was statistically significant (P = 0.001). Univariate correlation analysis has revealed a strong correlation between CIMT and age (r = 0.605 P < 0.000), BMI (r = 0.377, P = 0.002), Serum Cholesterol (r = 0.236. P= 0.018) and Serum Triglyceride levels (r = 0.387, P = < 0.001) and eGFR (r= -0.02, p <0.001).*

Conclusions: *Patients with CKD are associated with greater risk of atherosclerosis as compared to the general population. CIMT, used as a surrogate marker of atherosclerosis is significantly higher in CKD patients when compared to healthy controls. The exact pathogenesis of accelerated atherosclerosis in CKD patients is unclear but probably involves interplay of traditional and uremia related risk factors.*

Keywords: *carotid intima media thickness, Chronic kidney disease, glomerular filtration, rate atherosclerosis.*

INTRODUCTION

Chronic kidney disease (CKD) is a serious condition associated with premature mortality, decreased quality of life, and increased health-care expenditures. [1,2,3] The prevalence of end-stage renal disease continue to rise worldwide. Even more disturbingly, the current number of patients with early chronic kidney disease - the pool from which future end-stage renal disease patients will emerge exceeds the present number with end-stage renal disease by a factor of 30 to 60.[4,5] The burden of chronic kidney disease (CKD) in India cannot be assessed accurately. The approximate prevalence of CKD is 800 per million populations, and the incidence of end-stage renal disease (ESRD) is 150–200 pmp.[6] However, early chronic kidney disease will not progress to end-stage renal disease in all patients. Many patients with chronic kidney disease have cardiovascular disease and die prematurely from this condition instead of surviving long enough to face dialysis or transplantation[7,8]. Surveys showed that the risk for cardiovascular disease increases at much earlier stages of renal disease.[1,9] Furthermore, people with chronic kidney disease tend to have an excess of traditional risk factors for cardiovascular disease, such as hypertension, diabetes, and hyperlipidemia.7 Renal disease also engenders an environment that promotes cardiovascular injury in ways that are more or less specific to chronic kidney disease. Calcium and phosphorous dysregulation with vascular calcification, anemia, and hyperhomocysteinemia are among the often-cited cardiovascular liabilities of chronic kidney disease. [10,11,12] Most evidence about the nature of vascular disease association with renal disease comes from patients with end stage renal disease on dialysis. There is little information about how this disease evolves over in patients with progressive renal impairment and its co-relation with standard risk factor like dyslipidemia, diabetes and hypertension. This is more difficult to determine because the overt cardiovascular disease is less common in patients with mild renal impairment. Therefore this study is attempted to view the relationship between dyslipidemia and atherosclerosis in CKD patients. Atherosclerosis unless in a severe form is often asymptomatic, so that a direct examination of vessel wall is necessary to detect affected individuals in early stages. It has been suggested by International Atherosclerosis Project that atherosclerotic process occurs at the same time in carotid, cerebral and coronary arteries.[11] Carotid artery Intima Media Thickness (CA-IMT) is well-established index of systemic atherosclerosis that co-relate well with the incidence of coronary heart disease [12] and stroke[13] in non uremic population as well as uremic population.[14] Also studies have shown that CA-IMT is an independent predictor of cardiovascular mortality in hemodialysis population.[15,16]

Measurement of carotid intima – media thickness of the common carotid artery by B-mode ultrasound was found to be suitable noninvasive method to visualize the arterial walls and to monitor the early stages of atherosclerotic process.[17,18,19,20,21] Measurement of carotid intima media thickness is also helpful in clinical decision making, in assessing the best method of treatment,

either surgical or medical, in patients with carotid artery stenosis and also can be used to assess the effects of medical therapies of atherosclerosis. [19]

Methods

Seventy patients with a diagnosis of chronic kidney disease attending OPD of nephrology at Narayana Medical College & Hospital during the period September 2010 to December 2011 were undertaken for the study. The study protocol approved by Institutional Ethics Committee. Thirty age and sex matched controls were included in the study

Inclusion criteria

(1) Patient age greater than 18 years.

(2) Patient with chronic kidney disease defined by NKF/KDOQI guidelines.

Exclusion criteria

(1) Patient having diagnosed as ARF,

(2) History of carotid surgery/ IHD

(3) Smokers

(4) Patients on hemodialysis,/peritoneal dialysis

(5) Post renal transplant recipients

A complete clinical examination was done with special reference to signs of CKD and to rule out ischemic heart disease. Hypertension was defined as blood pressure >140/90 mm Hg or if patient is already on antihypertensive drug. All patients were investigated with complete hemogram, urine analysis, blood urea levels, serum creatinine levels and lipid profile (Total cholesterol, Triglycerides and HDL-C LDL-C VLDL-C) All the biochemical parameters were measured by standard laboratory technique. Glomerular filtration rate (GFR) was calculated by modification of diet in renal disease formula (MDRD) formula Measurement of Carotid Intima Media Thickness Carotid intima media thickness was measured by B mode ultrasound using a 7.5MHz transducer. Intima Media Thickness was defined as distance between leading edge of first echogenic line (Lumen – Intima interface) and second echogenic line (Media Adventitia interface) of far wall. Three measurements were taken 0.5, 1 and 2 cm below carotid bifurcation of common carotid artery on each side. The arithmetical averages of these were taken. The IMT of both sides (right and left) was calculated and average of these two values was taken and used for statistical analysis. CIMT measurement was always performed by single radiologist in plaque free arterial segments. The presence of plaques was noted. Plaques were defined as focal widening relative to the adjacent segment, with protrusion into the lumen. The site and extent of lesion were not quantified.

All parameters were expressed in mean values. Pair wise comparison between the cases and controls was done for all parameters using Students Unpaired t- test. The values of P which are < 0.05 were treated as significant. The qualitative variables (like sex) were compared using $\chi 2$ test. Univariate correlation analysis was used to confirm the significance of variables with CIMT. Statistical analysis done using SPSS version[13].

Results

Base line characteristics of the study population and controls are as shown in the following table 1.

The mean age was 44.55± 16.26 years and 45.66± 16.90 years in cases and controls respectively. Maximum number of subjects was in age group of 20-40 years. Thus, the age distribution between the two groups was not statistically significant (p = 0.986) and the two groups were matched with respect to age.

Table 1: Baseline characteristics of the study population

Parameter	CKD (n=70)	Controls (n=30)	P value
Sex (M/F)	39/31	17/13	
Mean Age (yrs)	44.55± 16.26	45.66± 16.90	0.986(NS)
BMI (kg/m)	22.65±2.98	23.35± 1.99	0.248(NS)
Blood Urea (mg/dl)	126.7± 79.35	28.8± 3.65	P<0.001(S)
S Creatinine mg/dl	7.8 ± 1.12	0.91±0.12	P<0.001(S)
TC (mg/dl)	204.18± 40.9	193.63± 25.95	P=0.196(NS)
TG (mg/dl)	176.74± 64.22	128.0± 15.39	P < 0.001(S)
HDL-C (mg/dl)	36.6± 9.48	40.93± 3.89	P < 0.018(S)
Serum Calcium (mg/dl)	8.23± 1.06	-	-
Serum Phosphorous(mg/dl)	5.3±1.51	-	-
CaxP (mg /dl)	43.5±12.69	-	-

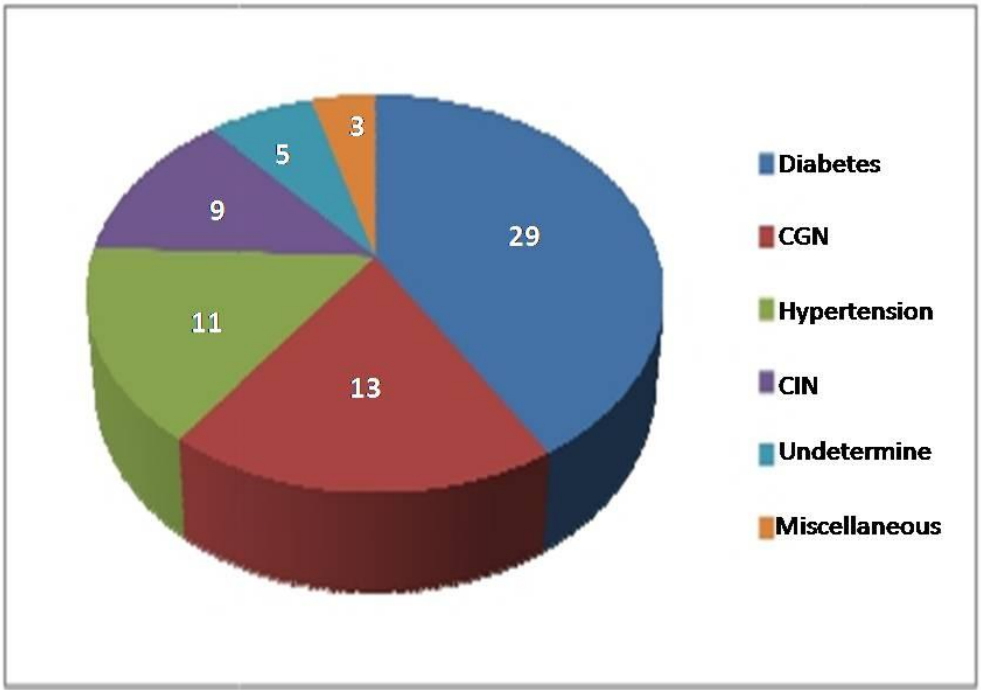

Figure 1: Native kidney disease of study population

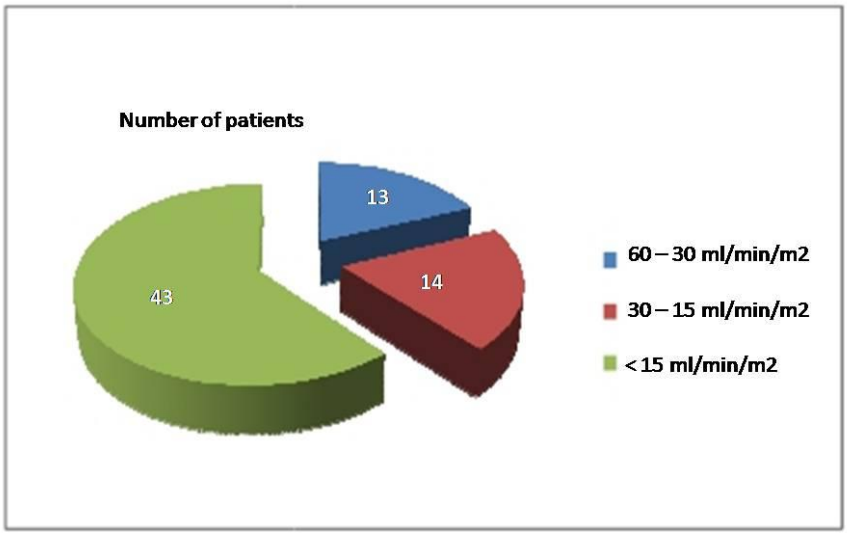

Figure 2. Distribution of subjects according to eGFR

In the present study, 39(55.7%) were males and 31 (44.3%) were females in the CKD cases group compared with 17 (56.7%) males and 13 (43.3%) females in control group. There was preponderance of males in both groups. This gender distribution revealed no significant difference between two groups (P = 0.930) and the two groups were matched with respect to gender.

NATIVE KIDNEY DISEASE OF CKD PATIENTS

In the present study, Diabetic Nephropathy (DN) was the leading cause for Chronic Kidney disease in 29 (41.4%) cases. CGN 13(18.6%) was second leading cause of chronic kidney disease. Hypertensive nephrosclerosis accounts for 11 (15.7%) cases of CKD. (Figure 1)

Distribution of subjects according to eGFR

The study populations were grouped in to three groups based on eGFR, using the modified MDRD formula. In the present study, 43 patients (61.43%) had eGFR < 15 ml/min/m2, 14 patients had eGFR between 30 and 15 ml/min and 13 patients had eGFR between 30 and 60 ml/min/m2. (Figure 2)

Carotid intimal media thickness in study population

The Carotid Intima Media Thickness (CIMT) ranged from 0.4 to 1.2mm in CKD patients compared to 0.4 to 1 mm in healthy controls. 42 CKD patients (60%) had high CIMT levels (i.e > 0.8 mm). When mean carotid intimal media thickness was compared between the cases and controls, there was a statistically significant (P < 0.001) difference in CIMT between the two groups. The mean CIMT in CKD patients was 0.86± 0.21 mm and that in healthy age and sex matched controls was 0.63± 0.17 mm. (Table 2 & Table 3)

Table 2. Distribution of subjects by Carotid Intima Media Thickness:

CIMT (mm)	Cases		Controls	
	CIMT (mm) No.	%	No.	%
< 0.4	0	0	2	6.7
0.41 – 0.80	27	38.6	23	76.7
0.81 – 1.20	42	60.0	5	16.7
>1.2	1	1.4	00	00
Total	70	100	30	100

Table 3. Comparison of CIMT value between cases and controls

CIMT(mm)	Cases	Controls	P value
Range	0.50-2.10 mm	0.4-1.00 mm	--
Right CIMT	0.85±0.21	0.63±0.16	<0.001
Left CIMT	0.86±0.21	0.64±0.18	<0.001
Mean CIMT	0.86±0.21	0.63±0.17	<0.001

When CIMT was compared between diabetic and non diabetic CKD patients there was a statistically significant (P < 0.01) difference in CIMT between the two groups. The mean CIMT in Diabetic CKD patient was 0.93± 0.25 mm and that in Non Diabetic CKD was 0.80± 0.14 mm. When CIMT values were compared among the groups of CKD based on eGFR using modified MDRD formula, in patients with eGFR < 15 ml/min/m2 the mean CIMT was 0.99mm and in patients with eGFR 30-15 ml/min/m2 was 0.85 mm and in patients with eGFR 30 – 60 ml/min/m2 was 0.74 mm. The correlation co efficient is 0.02 and is not significant (P = 0.03).

Correlation of CIMT to traditional risk factors and eGFR

When Univariate correlation analysis between CIMT and study parameters of Age, BMI, calcium-phosphorous product (CaxP) product, serum total cholesterol levels, serum triglyceride levels, serum HDL-C levels LDL-C and VLDL-C were performed in CKD patients, significant correlation (P <0.05) of CIMT was found with age, BMI ,Serum cholesterol and serum triglyceride levels and eGFR. (Table 4)

Table 4. Univariate Correlation Analysis of CIMT in CKD patients

Parameter	r (Correlation Coefficient)	P – value
Age	0.605	<0.001(HS)
BMI	0.377	<0.001(HS)
Calcium-Phosphorous Product	0.184	0.128(NS)
Serum Total Cholesterol	0.236	0.018(S)
Serum Triglyceride	0.387	<0.001(HS)
Serum HDL-C	0.191	0.057(NS)
Serum LDL	0.233	0.19(NS)
VLDL	0.08	0.398(NS)
eGFR (MDRD formula)	-0.02	P=0. 03(S)

DISCUSSION

In this study, seventy patients having chronic kidney disease (defined in accordance to NKF/ KDOQI guidelines) were studied for common carotid artery intimal-medial thickness in relation with the different stages of chronic kidney disease and also with cardiovascular risk factor like age sex BMI, Diabetes and Dyslipidemia. Thirty age and sex matched control were taken in the study. The study was carried out during the period September2010- December 2011.

The mean age was 44.55± 16.26 years(Range20-75) and 45.66± 16.90 years(Range20-75) in cases and controls respectively. Maximum numbers of subject were in age group of 20-30 years. There was a male preponderance in cases [n=39(55.7%)] as well as in controls [n=17(56.7%)]. It is generally believed that the atherosclerotic changes in the carotid artery mirror general atherosclerosis. High-resolution B mode ultrasound scan, a valid noninvasive method for assessment of asymptomatic atherosclerosis, has been widely used to study carotid atherosclerosis in the general population[14]. Ultrasound measurements of the intima media thickness (IMT) in the carotid arteries were used as an indicator of coronary therosclerosis [14, 15, 22]. In the present study, mean CIMT in CKD patients was 0.86± 0.21 mm and that in healthy age and sex matched controls was 0.63± 0.17 mm which is comparable with the study done by Shoji et al 28 who compared CIMT in 110 predialysis patients (0.889±0.035 mm) with normal healthy controls (0.685± 0.010 mm) and found CIMT was significantly (P <0.0001) raised in the predialysis CKD patients. Similar results were seen in other studies as shown in the following table 5.

Table 5: CIMT values in CKD patients in Different Studies

Study	No. of Cases	Mean Age (yrs)	Mean CIMT in CKD patients (in mm)	Mean CIMT in controls (in mm)	P values
Cheuk-Chun Szeto et al 22	203	53.8 ± 10.9	0.808 ± 0.196	-	-
Yilmaz et al 23	406	--	0.9	0.6	p <0.001).
Sunil kumar et al 24	30	--	1.0	0.73	(P <0.0036
A. Nakashima et al 25	112	55.8 ± 13.0	0746 ± 0.142	-	-
S. Brzosko et al 26	21	49.6 ± 16.7	0.76 ± 0.14	0.55 ± 0.07	P < 0.0001
Present study	70	44.55±16.26	0.86 ± 0.21	0.63 ± 0.17	P=0.001

The exact pathogenesis of increased atherosclerosis in chronic kidney disease is not exactly known but probably involves traditional and uremia related risk factors.[31] The present study showed a strong correlation between CIMT and age (r =0.605 P < 0.000).Similar results were seen in several other studies by Kawagishi et al [14], Cheuk Chun Szeto et al [22] (r = 0.373, P < 0.001), Bevc et al [27] (r = 0.589, P =0.0001), Brzosko et al26 and Shoji et al [27]. This reflects atherosclerosis increases with age. The present study also showed strong correlation between CIMT and BMI (r = 0.02 P = 0.002) similar results were obtained in a study by Brzosko et al).[26]

In the present study eGFR was calculated by MDRD formula and correlated with mean CIMT. Though mean CIMT was found to be higher in the late stages of kidney disease (eGFR < 15ml/min/m2) as compared to early stages (GFR > 30 ml/min/m2) there was no statistically significant difference between the two. But CIMT was significantly higher in patients with CKD at all stages compared to healthy control. This suggests that atherosclerosis starts at early stages of CKD. Also univariate correlation showed a significant correlation between eGFR and CIMT (r= -0.02, p <0.001) suggesting a role of reduced renal function in the pathogenesis of atherosclerosis. The reasons for the high atherosclerotic risk in patients with CKD remain unknown. A possible explanation is that decreased renal function may be associated with other non-traditional risk factors that were not evaluated in this study which include uric acid, homocysteine , C-reactive protein, albuminuria, oxidative stress, endothelial dysfunction and cytokines.[22, 29,30,31]

In the study by Shoji et al [27], no significant difference was found in CIMT between the CRF patient group and the hemodialysis patient group (p = 0.821). They concluded that atherosclerosis might be caused by renal failure and/or metabolic abnormalities secondary to renal failure.

Preston et al [32] reported that patients with stage 3 to 4 CKD had increased CIMT compared with normotensive volunteers. Lu Xia Zhang et al [33] in their study on stage 2-3 CKD patients (i.e., mild

and moderate renal insufficiency) found significantly increased CIMT in those patients and concluded that arterial change might occur in course of CKD earlier than previously believed. The present study showed a higher CIMT levels in diabetic CKD patients than in non diabetic CKD patients (0.93±0.25 vs 0.80±0.14 p <0.01). This observation is similar to the study by szeto et al [22.] Also univariate correlation analysis showed significant co relation of Serum Cholesterol (r = 0.236. P= 0.018) and Serum Triglyceride levels (r = 0.387, P = < 0.001) with CIMT values. In summary, Chronic kidney disease may be complicated by both traditional cardiovascular disease risk factors like age, diabetes, dyslipidemia etc and uremia related risk factors. The combined effect of these both type of risk factors lead to enhanced atherosclerosis in CKD patients as compared to the general population.

CONCLUSIONS

1. The mean carotid artery intimal -media thickness was significantly higher in patients with CKD when compared to age and gender matched healthy controls.
2. Carotid intima media thickness is higher at later stages of CKD compared to earlystages
3. Carotid intima media thickness has significantly positive correlation with traditional atherosclerotic risk factors like age, body mass index and serum triglyceride levels and serum cholesterol in CKD patients
4. Declining eGFR shows significant correlation with increased Carotid intima mediathickness values.
5. Carotid artery intimal medial thickness is a useful surrogate marker of atherosclerosis in CKD patients

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