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A Study of Carotid Intimal-Medial Thickness in Different Stages of Chronic Kidney Disease In Relation To Lipid Profile

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Abstract: *Chronic kidney disease (CKD) is a serious condition associated with premature mortality, decreased quality of life, and increased health-care expenditures. The prevalence of end-stage renal disease continues to rise worldwide.However, 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.Furthermore, people with chronic kidney disease tend to have an excess of traditional risk factors for cardiovascular disease, such as hypertension, diabetes, and hyperlipidemia.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.Carotid artery Intimal Medial Thickness (CIMT) is well-established index of systemic atherosclerosis that correlates well with the incidence of coronary heart disease and stroke in non-uremic population as well as uremic population.Also studies have shown that CA-IMT is an independent predictor of cardiovascular mortality in hemodialysis population.Measurement of carotid intima - media thickness of the common carotid artery by B-mode ultrasound was found to be suitable non-invasive method to visualize the arterial walls and to monitor the early stages of atherosclerotic process.In this study, we studied seventy patients with diagnosis of chronic kidney disease& aged more than 18 years admitted to medicine inpatient /outpatient departmentbetween April 2016 to October 2017 in Rajendra Institute of Medical Sciences, Ranchi.*
The study has shown significantly higher CIMT values in CKD patients as compared to age & gender matched controls.

I. 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 continues to rise world wide. 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 population (pmp), 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. Indeed, many will probably die of other conditions first. 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, and renal dysfunction itself, even at relatively high glomerular filtration rates.[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 nature of the vascular disease associate with renal disease come from pt with end stage renal disease on dialysis there is little information about how this diseases evolve over in patient with progressive renal impairement and whether it co-relate with standard risk factor like dyslipidemia, diabetes and hypertension. this 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 Intimal Medial Thickness (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 has 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 as to 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]

II. Material And Methods

The study was a cross sectional study and data was collected from April 2016 to October 2017 at Department of Medicine, Rajendra Institute of Medical Sciences, Ranchi.The study was carried out among seventy patients diagnosed with Chronic Kidney Disease.Thirty age and sex matched controls were also recruited. The study protocol was approved by the Institutional Ethics Committee.

Study Design: Cross Sectionalcase control study

Study Location: This was a tertiary care teaching hospital based study done in Department of Medicine, Rajendra Institute of Medical Sciences, Ranchi

Study Duration: April 2016 to October 2017

Sample size: 70 cases &30 controls

Sample size calculation: This was done using the Power/Sample size calculator, our sample size came out be 65 (taking a confidence interval of 95%, power of study as 90%, prevalence of CKD as 800 per million population (pmp).The study was carried out among seventy patients diagnosed with CKD. Thirty age and sex matched controls were also recruited.

Subjects & selection method

Cases:

USG proven Chronic Kidney disease patients matching the inclusion criteria were taken as cases.

Inclusion criteria:

1. Patient age greater than 18 years
2. Patient having chronic kidney disease

Exclusion criteria:

1. Patient having diagnosed as ARF
2. History of carotid surgery
3. Patient of age less than 18 years
4. Smokers
5. Pt who is on the hypolipidemic drugs
6. Patient having previous history of ischemic heart disease, myocardial infarction and stroke.

Controls:

Controls were primarily hospital based. Each control was matched for sex and age (±5 years). There was at least one control for each case recruited.

Inclusion criteria

1. Relative of a patient from ward.
2. Unrelated Visitor of any patient.
3. Patients attending the hospital or outpatient clinic for other illness.

Exclusion criteria

1. Any known kidney disease
2. Patients on nephrotoxic or hypolipidemic drugs.

Procedure methodology

Information was collected through prepared proforma for each patient and informed consent was obtained from each participant. The study protocol was approved by Institutional Ethics Committee of Rajendra Institute of Medical Sciences, Ranchi.

A complete clinical examination was done with special reference to signs of CKD like pallor, puffiness of face etc. and to rule out ischemic Heart disease.

Blood pressure was measured with standard mercury sphygmomanometer and cuff, after the subject had rested in supine position for 15 minutes. The systolic and diastolic blood pressure levels were taken as the

points of appearance and disappearance of Korotkoff sounds, respectively. Two measurements were taken with 10 minutes break and average of two measurements was taken as final value of blood pressure.

Hypertension was defined as blood pressure >140/90 mm Hg or if patient is already on antihypertensive drug.

Body Mass Index (BMI) was calculated according to the formula--- BMI= Weight (Kg)/ Height^2 (m).

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. The blood samples were drawn after 8 hours of overnight fasting. Glomerular filtration rate (GFR) was calculated by Cockcroft Gault equation and modification of diet in renal disease formula (MDRD) formula

Carotid intima media thickness was measured by B mode ultrasound using a 7.5 MHz 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.

Statistical analysis

For different parameters, mean and standard deviation were calculated. 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 X^2 test. The statistical software SPSS Ver.13 was used for statistical analysis. Univariate correlation analysis was used to confirm the significance of variables with CIMT.

III. Results

Table no 1:Distribution of the subject according to Stages of Chronic Kidney Disease (by CockCroft Gault formula)

In present study, when chronic Kidney disease patients were staged by Cockcroft gault formula. 38 (54.3%) patients were in stage 5, 15(21.4%) were in stage 4.

STAGES OF CKD (according to Cockcroft Gault)	**Cases**	**Percentage**
Stage 1	1	1.4
Stage 2	6	8.6
Stage 3	10	14.3
Stage 4	15	21.4
Stage 5	38	54.3
Total	70	100

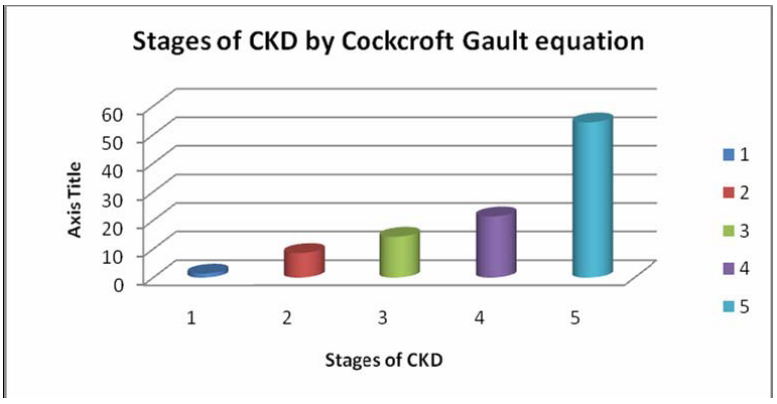


Table no. 2: Distribution of the subject according to Stages of Chronic Kidney Disease (by MDRD formula)
In present study, when chronic Kidney disease patients were staged by MDRD formula then 43 (61.4%) of the patients were in the stage 5, 14(20.0%) were in stage 4. 18.6% of the patients were in early stage of kidney disease (stage 1,2 and 3).

Stages of CKD (according to MDRD formula)	**Cases**	**Percentage**
Stage 1	1	1.4
Stage 2	6	8.6
Stage 3	6	8.6
Stage 4	14	20.0
Stage 5	43	61.4
Total	70	100

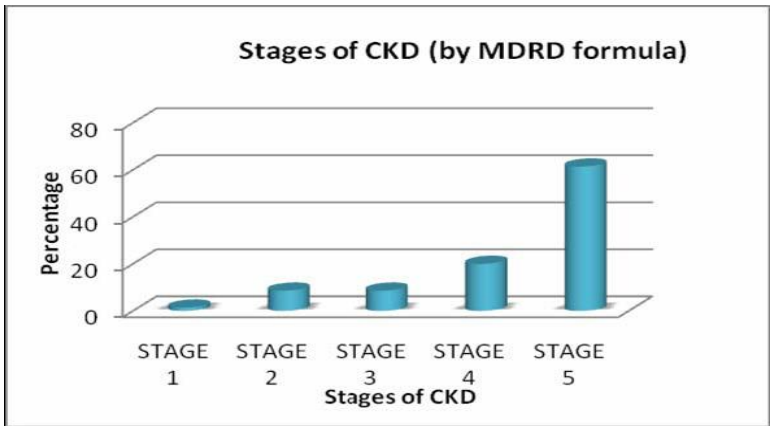


Table no. 3: Distribution of mean CIMT according to (eGFR) stage of CKD by CockCroft gault equation and MDRD formula
There is no direct co-relation of the CIMT and eGFR using Cockcroft Gault equation [CC= -0.130 (p=0.283)] and MDRD formula (CC=-0.02 (P=0.300).

Stages of CKD (according to MDRD formula)	**Mean CIMT**
Stage 1	0.58 mm
Stage 2	0.697 mm
Stage 3	0.895 mm
Stage 4	0.99 mm
Stage 5	0.845 mm
Correlation coefficient= 0.02	
p value = 0.300(NS)	

STAGES OF CKD (according to Cockcroft Gault)	**MeanCIMT**
Stage 1	0.58 mm
Stage 2	0.697 mm
Stage 3	0.886 mm
Stage 4	1.002 mm
Stage 5	0.83 mm
Correlation coefficient = 0.130	
p value=0.283(NS)	

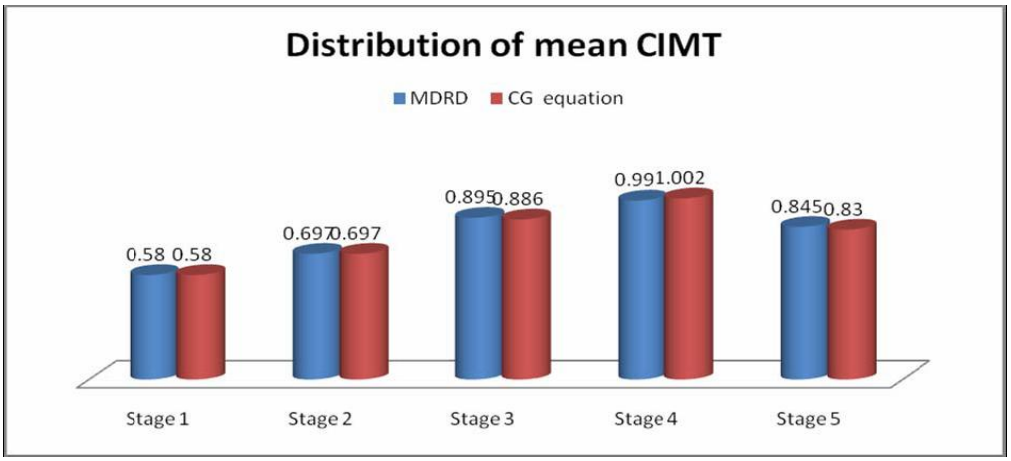


Table no4: Distribution of subjects by Serum Cholesterol Levels
The mean Serum Cholesterol level was 204.18±40.9 mg/dl and 193.63±25.95 mg/dl in CKD patients and healthy controls respectively. There was no statistically significant difference (p value = 0.196) in Serum Cholesterol levels between the two groups.

Serum Cholesterol (mg/dl)	**Cases**		**Controls**	
	No.	%	No.	%
< 200	41	58.6	20	66.7
200–239	13	18.3	9	30.0
≥240	16	22.9	1	3.3
Total	70	100	30	100
Range	120-312		140-240	
Mean	204.18		193.63	
S D	40.9		25.95	
p value = 0.196(NS)				

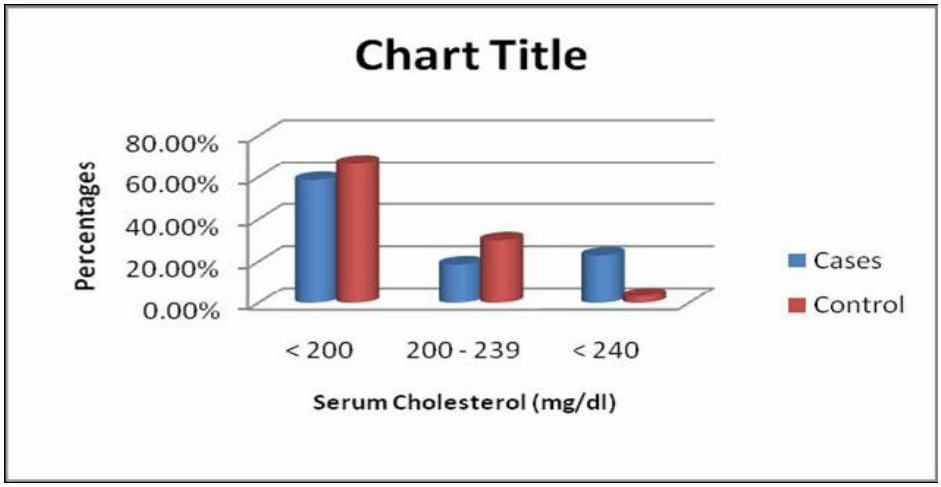


Table no. 5 : Distribution of subjects by Serum Triglyceride Levels
The mean Serum Triglyceride level was 176.74±64.22 mg/dl and 128.0±15.39 mg/dl in CKD patients and healthy control respectively. The difference in Serum Triglyceride levels was statistically significant (p < 0.001) between the two groups.

Serum Triglyceride (mg/dl)	**Cases**		**Controls**	
	No.	**%**	**No.**	**%**
< 150	28	40.0	29	96.7
151 – 200	25	35.7	1	3.3
201 – 300	13	18.6	0	0
>300	4	5.7	0	0
Total	70	100	30	100
Range	80-385		98-162	
Mean	176.74		128	
S D	64.22		15.39	
p value < 0.001 (significant)				

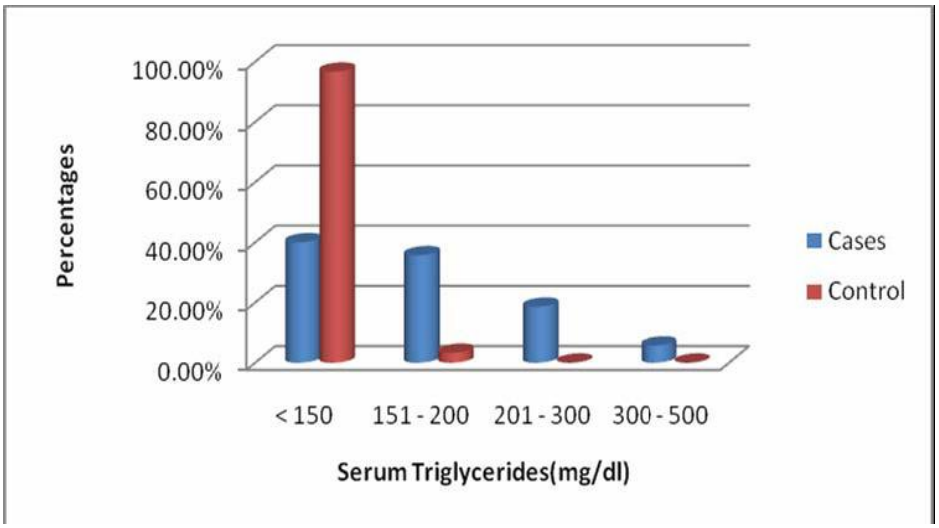


Table no.6 : Distribution of subjects by Serum High Density Lipid- Cholesterol Levels (HDL-C)
The Serum HDL-C levels in patients with CKD were 36.6±9.48 mg/dl and that in healthy controls was 40.93±3.89 mg/dl. The difference was statistically significant between the two groups (p < 0.018). 23(32.9%) CKD patients had Serum HDL-C levels below 30 mg/dl.

Serum HDL - C (mg/dl)	**Cases**		**Controls**	
	No	**%**	**No**	**%**
< 30	23	32.9	0	0
30 – 59	45	64.3	30	100
≥60	2	2.9	0	0
Total	70	100	30	100
Range	20-70		32-49	
Mean	36.6		40.933	
S D	9.484		3.89	
P value < 0.018 (Significant)				

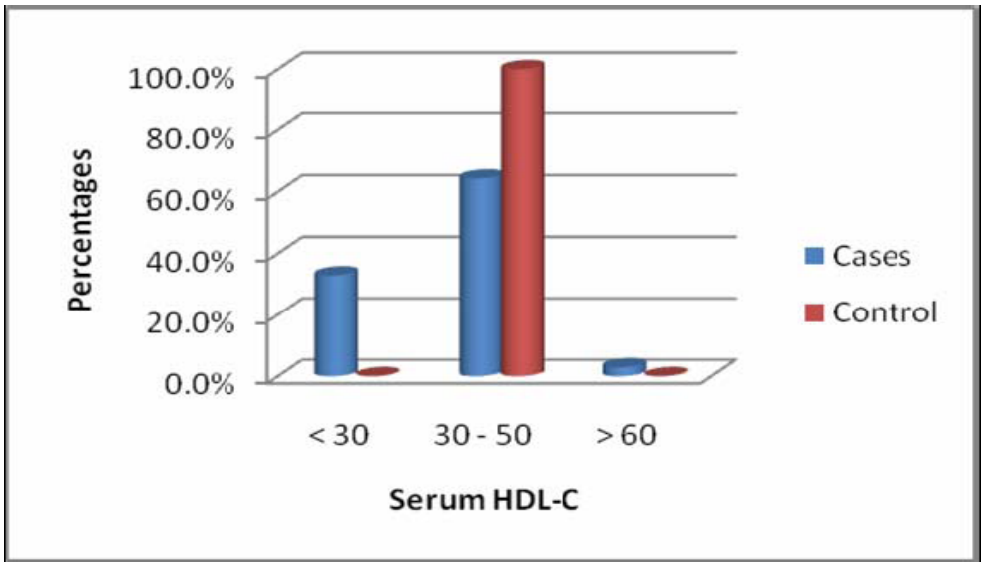


Table no. 7: Distribution of subjects by Carotid Intima Media Thickness

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).

CIMT (mm)	Cases		Controls	
	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
Range	0.50-2.10 mm		0.4-1.00 mm	
Mean	0.86 ±21 mm		0.64±0.18 mm	

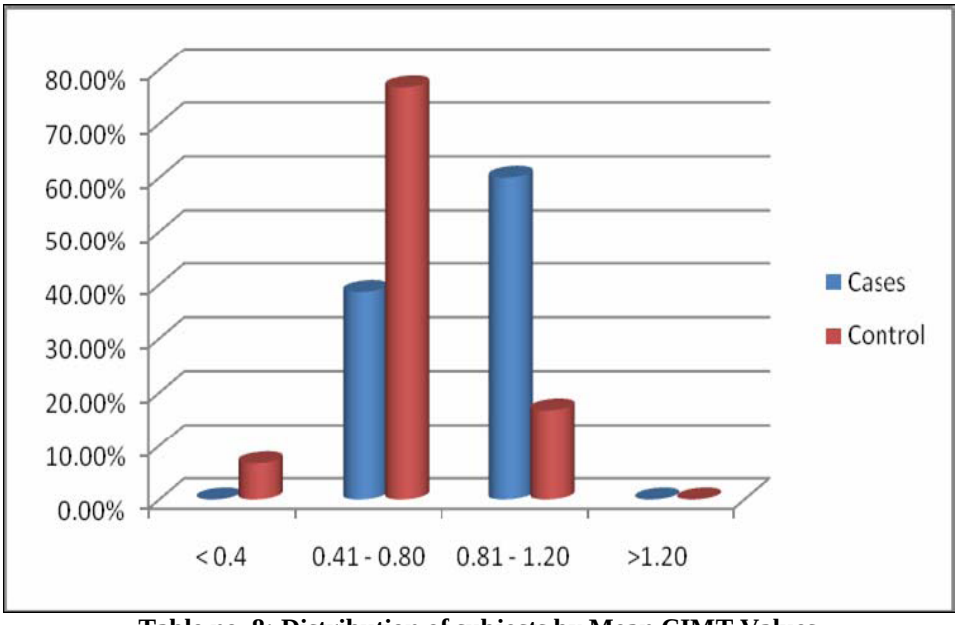


Table no. 8: Distribution of subjects by Mean CIMT Values

The mean CIMT in CKD patient was 0.86±0.21 mm and that in healthy age and sex matched controls was 0.63±0.17 mm. There was statistically significant ($p < 0.001$) difference in CIMT between the two groups.

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(S)
Left CIMT	0.86±0.21	0.64±0.18	<0.001(S)
Mean CIMT	0.86±0.21	0.63±0.17	<0.001(S)

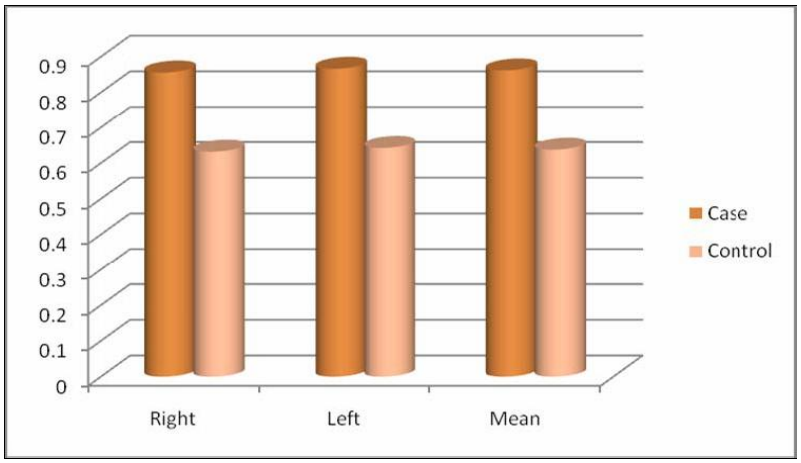


Table no. 9: Distribution of mean CIMT in Diabetic CKD and Non Diabetic CKD patients
The mean CIMT in Diabetic CKD patient was 0.93±0.25 mm and that in Non Diabetic CKD was 0.80±0.14 mm. There was statistically significant ($p < 0.01$) difference in CIMT between the two groups.

CIMT(mm)	Diabetic CKD	Non Diabetic CKD	p value
Right mCIMT	0.93 ±0.26	0.79±0.14	<0.006(HS)
Left mCIMT	0.93±0.25	0.81±0.15	<0.01(S)
Mean mCIMT	0.93±0.25	0.80±0.14	<0.01(S)

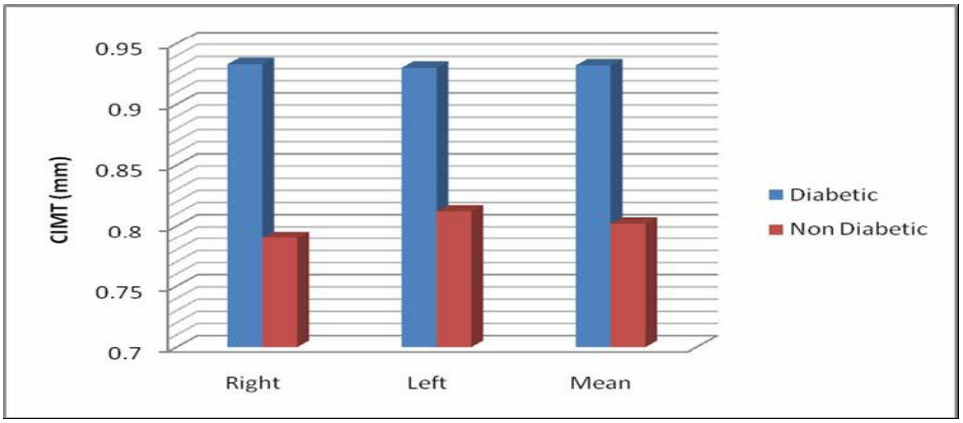
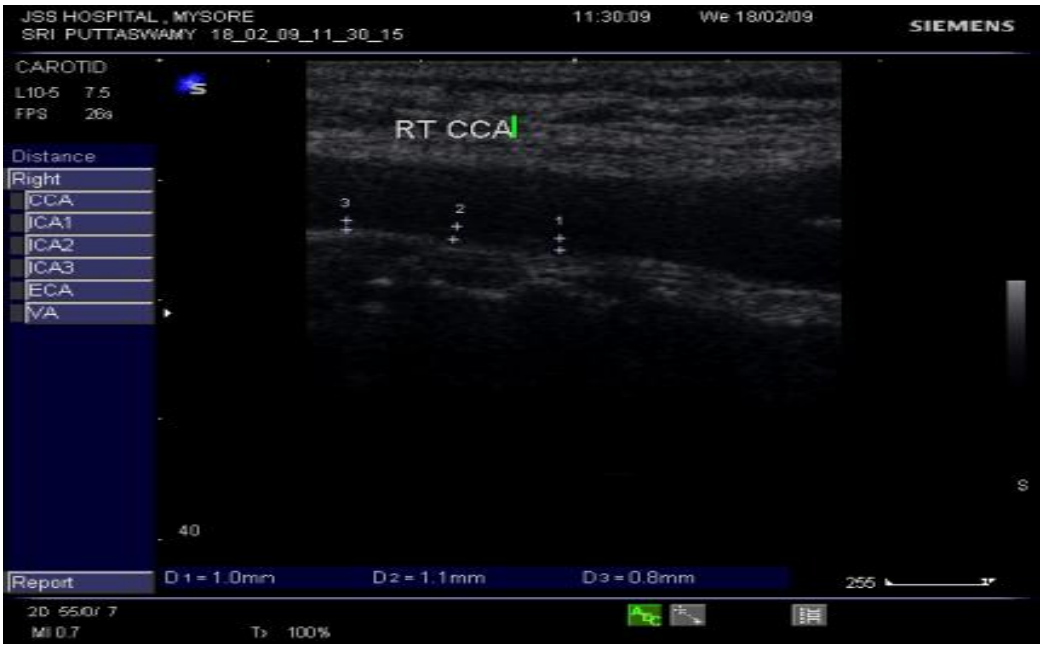


Figure 10 : CKD Patient In Study Group Having Significantly Thickened Right (A) And Left (B) CIMT



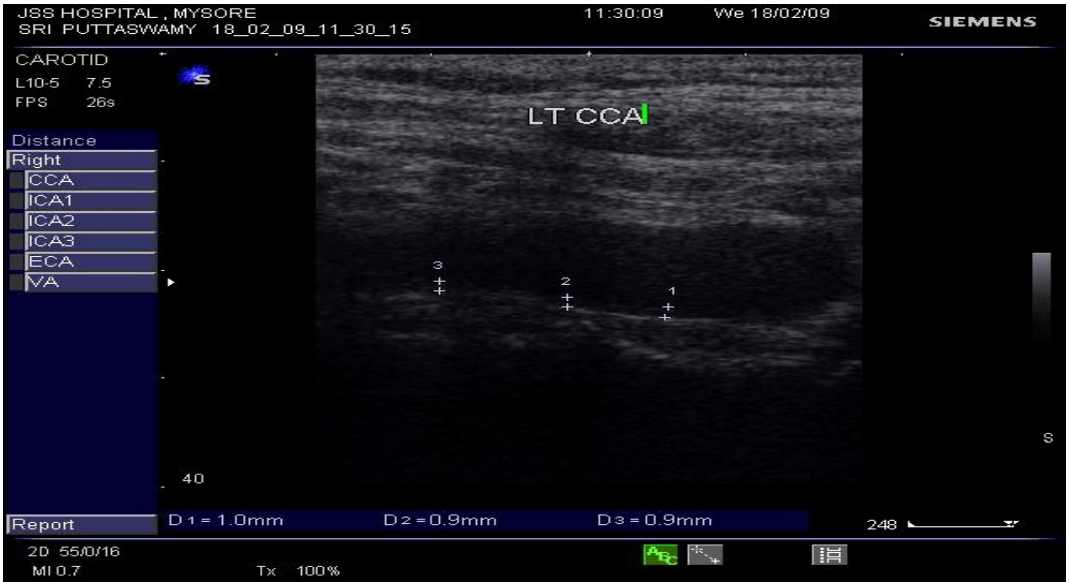


Table 11:. Univariate Correlation Analysis of CIMT in CKD patients

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.

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	0.019(NS)

VLDL	0.08	0.398(NS)
eGFR (Cockcroft gault Formula)	-0.130	p=0.283(NS)
eGFR(MDRD formula)	-0.02	p=0.300(NS)

IV. Discussion

In this study, seventy patients having chronic kidney disease (according to National kidney foundation) 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 a period of two years from September 2008 to November 2010. Studied population was satisfying the inclusion and exclusion criteria.

The mean age was 44.55±16.26 years (range 20-75) and 45.66±16.90 years (range 20-75) in cases and controls respectively. Maximum number of subject was in age group of 20-30 years. There was male preponderance in cases [n=39(55.7%)] as well as control [n=17(56.7%)] .

In present study, Mean CIMT in CKD patient 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 study done by Shoji et al [106] who studied CIMT in 110 patient predialysis patients (0.889±0.035 mm) with normal healthy controls (0.685± 0.010 mm) in which CIMT was significantly, (p <0.0001) raised

The present study showed a strong correlation between CIMT and age (r = 0.605, p < 0.000).Similar result were seen in several other studies by Kawagishi[14] et al, Cheuk Chun Szeto et al[105] (r = 0.373, p < 0.001), Bevc et al[104] (r = 0.589, p = 0.0001), Brzosko et al[109] and Shoji et al[106]. This reflects the atherosclerosis increase with age.

The present study showed strong correlation between CIMT and BMI (r = P = 0.002) similar results were obtained in a study by Brzosko et al [109](r = 0.50, p = 0.02).

In present study eGFR is calculated by both formula i.e. Cockcroft Gault equation and MDRD formula and correlated with mean CIMT. Though mean CIMT was found to be higher in the late stages of kidney disease (stage 4 and Stage 5) as compared to early stages(stage 1,2 and 3) there was no statistically significant difference between two. Again CIMT is not correlated with eGFR calculated by using Cockcroft Gault equation as well as using MDRD formula. But CIMT was significantly higher in th patient with CKD at all stages compared to healthy control. This suggest that atherosclerosis is started at early stages of CKD

In study by Shoji et al[106], no significant difference was found in CIMT between CRF patient group and hemodialysis patients group (p = 0.821). They concluded that atherosclerosis might be caused by renal failure and/or metabolic abnormalities secondary to renal failure.

Prestonet al[101] reported that patients with stage 3 to 4 CKD had increased CIMT compared with normotensive volunteers. Lu Xia Zhang et al[99] 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.

In present study, serum triglyceride levels were significantly (p<0.001) high in patients (mean=176.74±64.22) mg/dl in comparison with controls (128.0±15.39 mg/d). Similar results were obtained in study by Kawagishi[14] et al and Brzosko[109] et al.

In present study, serum Cholesterol levels were high in Chronic kidney disease (mean= 204.18±40.9 mg/dl) patients compared to control subjects (mean=193.63±25.95). But there was no statistically significant difference (p value = 0.196). Attmanet al[110] in their study showed no significant change in levels of total cholesterol. Similar results were obtained in study by Kawagishi[14] et. al. Thomas Quasctining et al[111] reported combined hyperlipidemia (elevated total cholesterol and triglycerides) in their study.

In present study, serum HDL were low in Chronic kidney disease (mean= 36.6±9.48 mg/dl) patients compared to control subjects (mean= 0.93±3.89 mg/dl). The difference was statistically significant between the two groups (p<0.018). P.O. Attmanet al[110]found decrease in plasma HDL cholesterol concentration in patients with Chronic kidney disease patient. Preston[101] et al and Shoji[106] et al showed similar result In the present study, significant correlation by Univariate analysis was found between serum Triglyceride levels, serum Cholesterol and CIMT in CKD patients but no correlation was obtained with CIMT and HDL-C levels.

The serum concentrations of lipids and lipoproteins has been related to carotid atherosclerosis in most studies (Bevc[104]et al, Brzosko et al, Kumbhalkar[112] et al, Shoji[106] et al) but not in all reports (Kawagishi et al, Cheuk Chun Szeto[105] et al, A. A. Kiykim[113] et al).

In the present study, 11 (15.7%) CKD patients had high calcium phosphorous product. There was no significant correlation seen with CIMT and CaxP product in CKD patients. These results are comparable with studies by Cheuk Chun Szeto[105] et al and Kiykim[113] et al where no correlation of CIMT with CaxP product was seen.

Summary of the study:

The present study included 70 CKD patients; 39 male and 31 female CKD patients. Also 30 age and sex matched controls were included in the study.
The mean age of CKD patients was 44.55±16.26 years and that of control group was 45.66±16.9 years.
Diabetes was the etiology of CKD in 29 (41.4%) patients. Chronic glomerulonephritis in 13 (18.6%) and Essential Hypertension in 11(15.7%) were other major causes of CKD patients.
The mean BMI was 22.65±2.98 kg/m2 in CKD patients and 23.35±1.99 kg/m2 in control group.
Most of the CKD patients in the present study was in Stage 5 i.e 43(61.4%).
Hypocalcaemia (< 9 mg/dl) was seen in 65(93%) CKD patients.
Hyperphosphatemia (> 5.5 mg/dl) was seen in 23(32.9%) CKD patients.
High calcium- phosphorous product was seen in 11 (15.7%) CKD patients.
High Total serum Cholesterol levels (>240 mg/dl) was found in 16 (22.9%) cases.
The mean Serum Triglyceride levels were significantly higher in CKD patients compared to control subjects.
The mean HDL-C levels were lower in patients compared to controls.
The mean CIMT was 0.86±0.21 mm in CKD patients compared to 0.63±0.17 mm in control subjects. Mean Carotid Intima Media Thickness was significantly more in CKD patients.
Mean CIMT in CKD patients significantly correlated with Age ($p< 0.001$), Body Mass Index ($p<0.001$), serum Triglyceride levels ($p< 0.001$) and serum Cholesterol ($p=0.018$) However, no correlation of CIMT was seen with calcium- phosphorous product, serum HDL-C, VLDL-C and LDL.
Mean CIMT was not directly correlating with eGFR. (Stages of Kidney Disease)

V. Conclusion

In present study, the mean carotid artery intimal -media thickness was significantly higher in patients with CKD when compared to age and gender matched healthy controls.
There is no significant co-relation of stage of kidney disease and CIMT.
It was also observed that carotid intimal media thickness significantly positive correlation with traditional atherosclerotic risk factors like age, body mass index and serum triglyceride levels and serum cholesterol in CKD patients.

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