

# Study of Carotid Intimal Medial Thickness in Chronic Kidney Disease at Rural Teaching Hospital

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## Abstract

**Background:** Patients with Chronic Kidney Disease (CKD) are associated with increased morbidity, mortality, and increased healthcare expenditures as they are at high risk for developing cardiovascular disease (CVD). Carotid intimal medial thickness (CIMT) has been found to correlate with atherosclerosis major risk factors of CVD. **Method:** This was a prospective case control study of carotid intimal medial thickness in patients of CKD. A total of 150 patients of CKD and equal number of age and sex matched controls were enrolled. Bilateral assessment of intimal medial thickness was done in common carotid artery. Statistical analysis was done by using descriptive and inferential statistics using the Chi square test, z-test for difference between two means, Pearson's Correlation coefficient and Multiple Regression Analysis and software used in the analysis were the SPSS 22.0 version. **Results:** Out of total 300 cases, 114 (76%) patients of CKD and 113 (75.33%) control were male. CIMT in CKD patients was between  $0.80 \pm 0.28$  mm and  $0.64 \pm 0.16$  in control  $p=0.0001$ . CKD patients with diabetes were having mean CIMT  $1.09 \pm 0.22$  mm in comparison to controls with diabetes having mean CIMT  $0.63 \pm 0.16$  mm,  $p=0.0001$ . CKD patients with hypertension were having mean CIMT  $0.76 \pm 0.27$  mm in comparison to controls having mean CIMT  $0.62 \pm 0.18$  mm,  $p=0.0001$ . **Conclusion:** Mean CIMT was increased in all stages of CKD and there was no significant difference in CIMT in different stages of CKD. Patients having hypertension was having higher mean CIMT in comparison to patients having normal blood pressure, patient with diabetes had high mean CIMT as compared to mean CIMT of controls having diabetes.

**Keywords:** Chronic kidney disease; Cardiovascular disease; Carotid intima media thickness; Atherosclerosis; Diabetes; Risk factors

## Introduction

Chronic kidney disease (CKD), refer to an irreversible deterioration in renal function which usually develop over a period of year. CKD are associated with increased morbidity and mortality, decreased quality of life and increased healthcare expenditures.<sup>[1-3]</sup> The prevalence of end-stage renal disease continues to rise worldwide. About 8.2 million Americans are at risk for moderate to severe CKD and even more worse, the current number of patients with early CKD - 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.<sup>[4, 5]</sup> The burden of CKD in India cannot be assessed accurately due to lack of proper data. The approximate prevalence of CKD is 800 per million population and more than 100, 000 new patients enter renal replacement programs annually in India.<sup>[6]</sup>

Atherosclerosis unless in a severe form is often asymptomatic, so that a direct examination of the vessel wall is necessary to detect affected individuals in the early stages.<sup>[7, 8]</sup> Atherosclerosis is the most common risk factors of cardiovascular morbidity in CKD patients.<sup>[8]</sup> Atherosclerotic changes in carotid arteries are assumed to be indicative of atherosclerosis throughout the body and peripheral arteries. It has been suggested by the International Atherosclerosis Project that the atherosclerotic process occurs at the same time in carotid, cerebral and coronary

arteries.<sup>7</sup> Carotid artery intimal medial thickness (CIMT) is well-established index of systemic atherosclerosis that correlate well with the incidence of coronary heart disease and stroke in non-uremic population as well as uremic population.<sup>[8-10]</sup>

Measurement of CIMT 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 the atherosclerotic process.<sup>[11-17]</sup> Measurement of CIMT 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.<sup>[15]</sup>

## Materials and Methods

### Study design and settings

This prospective case control study was carried out in the Department of Medicine, Acharya VinobaBhave Rural Hospital (AVBRH) of Jawaharlal Nehru Medical College, Wardha. All

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consecutive patient of CKD as well as same number of age and sex matched controls were included in the study after institute ethical committee clearance between the periods of 2014 to 2016. Patient having diagnosed as acute kidney injury, history of carotid surgery and ageless than 12 years were excluded from the study

### Sample size

150 cases of CKD diagnosed by above mentioned inclusion criteria and same number age and sex matched healthy control were included in the study.

### Methods

Demographic records (information comprised of sex, age, and address) and information about, alcohol use, smoking and history of all patients were collected. Written informed consent in English and local language was taken from the cases after explaining the nature of the evaluation to them. Each person was subjected to a thorough history and physical examination. A complete clinical examination was done with special reference to signs of CKD like pallor, puffiness of face etc.

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 at the points of appearance and disappearance of korotk off sounds, respectively. Two measurements were taken with 10 minutes break and average of the two measurements was taken as the final value of blood pressure. Hypertension was defined as blood pressure  $>140/90$  mm Hg or if the patient is already on antihypertensive drug.

All patients were investigated with complete hemogram, urine analysis, blood urea levels, serum creatinine levels and lipid profile. All the biochemical parameters were measured by standard laboratory technique. The blood samples were drawn after 10-12 hours of overnight fasting. Glomerular filtration rate (GFR) was calculated by modification of diet in renal disease formula (MDRD) formula. Complete blood count was done by counter report.

Under all aseptic precautions blood sample was collected from the vein of the subjects in plain bulb. All biochemical parameters were analyzed by RANDOX DAYTONA (Japan) random analyser by turbidimetry.

Fasting venous sample were taken from the vein and collected in plain bulb for serum total cholesterol, triglycerides, HDL which was estimated by using Liquid Stable CHOD – PAP method by Robonic Semiautomatic Chemical Analyser.

All cases underwent Ultrasound of the abdomen for kidney size, which was performed by a single experienced radiologist who was blind to the study.

### 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 the distance between the leading edge of the

first echogenic line (Lumen – Intima interface) and second echogenic line (Media – Adventitia interface) of the far wall. Three measurements were taken 0.5, 1 and 2 cm below the 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 the average of these two values was taken and used for statistical analysis. CIMT measurement was always performed by a 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 methods

Statistical analysis was done by using descriptive and inferential statistics using the Chi square test, z-test for difference between two means, Pearson's Correlation coefficient and Multiple Regression Analysis and software used in the analysis were the SPSS 22.0 version, GraphPad 6.0 version and EPI-INFO 6.0 version and  $p<0.05$  is considered as level of significance. Univariate correlation analysis was used to confirm the significance of variables with CIMT.

### Observations and Results

In this study out of 300 cases, 114 (76%) cases of CKD were males and 36 (24%) were females, whereas 113 (75.33%) were males and 37 (24.67%) were females in the control groups. Mean age of CKD was  $46.87 \pm 14.23$  years and control was  $47.15 \pm 14.12$  years, with age range from 17 to 80 years in case and 16-80 years in control groups. Maximum number of subjects was in the age group 41-60 years in both cases (47.33%) and controls (47.33%). Base line characteristics of the patients are shown in Table 1.

**Table 1: Baseline characteristics of study population.**

	Case Group (n=150)	Control Group (n=150)	P-value
Age (yrs)	$46.87 \pm 14.23$	$47.15 \pm 14.12$	0.864, NS
Gender			
Male	114 (76%)	113 (75.33%)	0.89, NS
Female	36 (24%)	37 (24.67%)	
DM	55 (36.67%)	50 (33.33%)	0.62, NS
HTN	93 (62%)	83 (55.33%)	0.29, NS
Alcohol	32 (21.33%)	25 (16.67%)	0.37, NS
Smoker	36 (24%)	30 (20%)	0.48, NS
TCH	$211.66 \pm 36.10$	$194.32 \pm 34.12$	0.0001, S
HDL-C	$39.34 \pm 12.72$	$42.95 \pm 8.90$	0.005, S
TG	$154.48 \pm 40.30$	$118.04 \pm 38.1$	0.0001, S
CIMT Lt Side	$0.81 \pm 0.31$	$0.63 \pm 0.17$	0.0001, S
CIMT Rt Side	$0.78 \pm 0.26$	$0.64 \pm 0.16$	0.0001, S
Mean CIMT	$0.80 \pm 0.28$	$0.64 \pm 0.16$	0.0001, S

Left CIMT in CKD group was  $0.81 \pm 0.31$  mm and  $0.63 \pm 0.17$  mm in control group ( $z=6.12$ ,  $p=0.0001$ ). Right CIMT in CKD group was  $0.78 \pm 0.26$  mm and  $0.64 \pm 0.16$  mm in control group ( $z=5.49$ ,  $p=0.0001$ ). The mean CIMT in CKD patient was  $0.80 \pm 0.28$  mm and that in healthy age and sex matched controls was  $0.64 \pm 0.16$  mm. There was statistically significant ( $\chi^2=33.88$ ,  $P<0.0001$ ) difference in CIMT between the two groups. [Tables 1 and 2] The mean CIMT in CKD stage 1 was  $0.70 \pm 0.26$  mm, stage 2 was  $0.81 \pm 0.30$  mm, stage 3 was  $0.80 \pm 0.29$  mm,

stage 4 was  $0.80 \pm 0.27$  mm, and stage 5 was  $0.83 \pm 0.29$  mm. There is no direct co-relation of the CIMT and stages of CKD (Correlation Coefficient ' $r$ '=0.119,  $p$ =0.146) [Table 3].

**Table 2: Distribution of patients by carotid intimal medial thickness.**

CIMT	Cases (n=150)	Controls (n=150)		
	N	%	N	%
$\leq 0.50$	34	22.67	46	30.67
0.51-0.80	63	42	91	60.67
0.81-1.20	33	22	12	8
>1.2	20	13.33	1	0.67
Total	150	100	150	100
Mean $\pm$ SD	$0.80 \pm 0.28$ (0.40-1.45)	$0.64 \pm 0.16$ (0.40-1.50)		
$\chi^2$ -value	33.88, $p$ =0.0001, S			

**Table 3: Distribution of mean CIMT according to stages of CKD.**

Stages of CKD	No of Cases	Mean CIMT
Stage 1	20	$0.70 \pm 0.26$ mm
Stage 2	12	$0.81 \pm 0.30$ mm
Stage 3	40	$0.80 \pm 0.29$ mm
Stage 4	30	$0.80 \pm 0.27$ mm
Stage 5	48	$0.83 \pm 0.29$ mm
Total	150	$0.80 \pm 0.28$ mm
Correlation Coefficient ' $r$ '	0.119	
$p$ -value	0.146, NS, $p$ >0.05	

55 cases of CKD were diabetic in the age group of 41-60 years in both cases (49.09%) and controls (44%). The mean CIMT in Diabetic CKD patient was  $1.09 \pm 0.22$  mm and that in Non-Diabetic CKD was  $0.63 \pm 0.16$  mm. Left CIMT in diabetic CKD group was  $1.14 \pm 0.23$  mm and  $0.62 \pm 0.17$  mm in non-diabetic CKD group ( $z=15.53$ ,  $p$ =0.0001). Right CIMT in diabetic CKD group was  $1.03 \pm 0.22$  mm and  $0.64 \pm 0.15$  mm in non-diabetic CKD group ( $z=12.57$ ,  $p$ =0.0001). There was statistically significant ( $P<0.0001$ ) difference in CIMT between the two groups [Table 4].

**Table 4: Distribution of mean CIMT in diabetic and non-diabetic CKD patients.**

CIMT	Diabetic CKD (n=55)	Non Diabetic CKD (n=95)	z-value	p-value
Range of CIMT	0.60-1.50	0.40-1.20		
Left CIMT	$1.14 \pm 0.23$	$0.62 \pm 0.17$	15.53	0.0001, S
Right CIMT	$1.03 \pm 0.22$	$0.64 \pm 0.15$	12.57	0.0001, S
Mean CIMT	$1.09 \pm 0.22$	$0.63 \pm 0.16$	14.25	0.0001, S

The mean Serum Cholesterol level was  $211.16 \pm 36.10$  mg/dl and  $194.32 \pm 34.12$  mg/dl in CKD patients and healthy controls respectively. There was statistically significant difference in Serum Cholesterol levels between the two groups ( $\chi^2=41.86$ ,  $p$ =0.0001). Serum HDL-C levels in patients with CKD was  $39.34 \pm 12.72$  mg/dl and that in healthy controls was  $42.95 \pm 8.90$  mg/dl. The difference was statistically significant between the two groups ( $\chi^2=6.54$ ,  $p$ =0.010). The mean Serum Triglyceride level was  $154.48 \pm 40.30$  mg/dl and  $118.04 \pm 38.01$  mg/dl in CKD patients and healthy control respectively. The difference in Serum Triglyceride levels was statistically significant between the two groups ( $\chi^2=18.87$ ,  $p$ =0.0001).

The mean CIMT of CKD and control with risk factor was studied. The mean CIMT of case and the control in Diabetic patient was  $1.09 \pm 0.22$  mm and  $0.60 \pm 0.12$  mm, There was statistically significant difference between the two groups ( $z=13.35$ ,  $p$ =0.0001). The mean CIMT of case and the control in hypertensive patient was  $0.76 \pm 0.27$  mm and  $0.62 \pm 0.18$  mm, There was statistically significant difference between the two groups ( $z=3.87$ ,  $p$ =0.0001). The mean CIMT of case and the control in alcoholic patient was  $0.73 \pm 0.26$  mm and  $0.64 \pm 0.24$  mm, There was no statistically significant difference between the two groups ( $z=1.35$ ,  $p$ =0.180). The mean CIMT of case and the control in smoker was  $0.83 \pm 0.28$  mm and  $0.62 \pm 0.14$  mm, There was statistically significant difference between the two groups ( $z=3.80$ ,  $p$ =0.0001) [Table 5]. On multiple regression analysis it was found that CIMT and other risk factor like age, gender and DM are independent variables and other risk factors like HTN, alcohol, smokers and dyslipidemia are dependent to each other [Table 6].

**Table 5: Distribution of mean CIMT with risk factors.**

	Cases Mean CIMT (mm)	Control Mean CIMT (mm)	z-value
Diabetes Mellitus	$1.09 \pm 0.22$	$0.60 \pm 0.12$	13.35 $p$ =0.0001, S
Hypertension	$0.76 \pm 0.27$	$0.62 \pm 0.18$	3.87 $p$ =0.0001, S
Alcohol	$0.73 \pm 0.26$	$0.64 \pm 0.24$	1.35 $p$ =0.180, NS
Smoker	$0.62 \pm 0.18$	$0.62 \pm 0.18$	$0.62 \pm 0.18$

**Table 6: Multiple regression analysis.**

	Unstandardized Coefficients	Standardized Coefficients	t	p-value
	B	Std. Error		
CIMT	1.209	0.192		
Age	0.003	0.001	0.160	2.683 0.008, S
Gender	0.087	0.040	0.128	2.187 0.030, S
Stages of CKD	-0.009	0.014	-0.042	0.628 0.531, NS
DM	-0.426	0.033	-0.711	12.814 0.0001, S
HTN	0.052	0.034	0.087	1.536 0.127, NS
Alcohol	0.028	0.040	0.040	0.709 0.480, NS
Smoker	-0.036	0.040	-0.053	0.910 0.364, NS
TC	-6.001	0.001	-0.007	0.110 0.913, NS
HDL	0.000	0.001	-0.027	0.426 0.671, NS
LDL	0.000	0.001	-0.013	0.217 0.829, NS
VLDL	0.000	0.003	-0.015	0.243 0.808, NS
TG	0.000	0.000	0.059	0.945 0.347, NS

## Discussion

This study of hospitalized patients of CKD as well as age and sex matched control from rural Central India points to a possible correlation between CIMT and cardiovascular risk factors. In this study, maximum number of subjects was in the age group 41-60 years in both cases (47.33%) and controls (47.33%). The

**Table 7: Various studies of CIMT with CKD.**

<b>Study</b>	<b>No. Of Cases</b>	<b>Mean Age (yrs)</b>	<b>Mean CIMT in CKD patients (in mm)</b>	<b>Mean CIMT in controls (in mm)</b>	<b>P-values</b>
Szeto et al. [18]	203	53.8 ± 10.9	0.808 ± 0.196	-	P<0.0001
Brzosko et al. [20]	21	49.6 ± 16.7	0.76 ± 0.14	0.55 ± 0.07	P<0.0001
Nakashima et al. [23]	112	55.8 ± 13.0	0746 ± 0.142	-	P<0.0001
Sunil Kumar et al. [24]	30	-	1	0.73	P<0.0036
Yilmaz et al. [25]	406	-	0.9	0.6	p<0.001
Present study	300	46.87 ± 14.23	0.80 ± 0.28	0.64 ± 0.16	P<0.0001

mean age was  $46.87 \pm 14.23$  years and  $47.15 \pm 14.12$  years in cases and controls respectively.

This study showed a strong correlation between CIMT and age ( $r=0.267$  P - 0.001). Similar result was seen in several other studies by Kawagishi et al., [10]. Szeto CC et al. [18] ( $r=0.373$ ,  $P<0.001$ ), Shoji et al., [19]. Brzosko et al. [20]. Preston et al. [21] and Lemos et al. [22]. This reflects the atherosclerosis increase with age.

Mean CIMT in our CKD patient was  $0.80 \pm 0.28$  mm and that in healthy age and sex matched controls were  $0.64 \pm 0.16$  mm, which was comparable with study done by Shoji et al. [19] who studied CIMT in 110 patient ( $0.889 \pm 0.035$  mm) with normal healthy controls ( $0.685 \pm 0.010$  mm) in which CIMT was significantly, ( $P<0.0001$ ) raised. Comparison of other studies of CIMT with CKD are shown in Table 7.

In the present study CIMT was not correlated with the stages of CKD, [23-25] but it was significantly higher in the patient with CKD at all stages compared to healthy control. Mean CIMT were increased as stages progressed, e.g. in stage 1;  $0.70 \pm 0.26$  mm, stage 2;  $0.81 \pm 0.30$  mm, stage 3;  $0.80 \pm 0.29$  mm, stage 4;  $0.80 \pm 0.27$  mm and stage 5;  $0.83 \pm 0.29$  mm. Lu Xia Zhang et al. [26] found significantly increased CIMT in stage 2-3 CKD patients and concluded that arterial change might occur in the course of CKD earlier than previously believed. Preston et al. [21] reported that patients with stage 3 to 4 CKD had increased CIMT compared with normotensive volunteers. Arun kumar Ponna et al. [27] found increased CIMT in all the stages of CKD.

In the present study, serum triglyceride levels were significantly ( $p<0.0001$ ) high in patients (mean= $154.48 \pm 40.30$  mg/dl in comparison with controls ( $118.04 \pm 38.01$ ) mg /dl. Similar results were obtained in study by Kawagishi et al. [10] and Brzosko et al. [20]. Serum Cholesterol levels were high in Chronic kidney disease (mean= $211.16 \pm 36.10$  mg/dl) patients compared to control subjects (mean= $194.32 \pm 34.12$ ), ( $P$  value= $0.0001$ ). Brzosko et al. [20] and Arun Kumar et al. [27] showed significant change in levels of total cholesterol. In present study, serum HDL were low in CKD (mean= $39.36 \pm 12.72$  mg/dl) patients compared to control (mean= $42.95 \pm 8.90$  mg/dl). The difference was statistically significant between the two groups ( $P=0.010$ ). Shoji et al. [19] and Preston et al. [21] also showed significant changes in level of serum HDL-C.

In our study, 55 cases of CKD were diabetes compare to 50 were control with mean of  $48.48 \pm 12.84$  and  $46.27 \pm 13.37$  respectively. In present study, 93 cases of CKD were hypertensive compared to 83 were control with a mean of  $48.48 \pm 12.84$  and  $46.27 \pm 13.37$  respectively. The mean CIMT of

diabetic case and the control was  $1.09 \pm 0.22$  mm and  $0.60 \pm 0.12$  mm, ( $z=13.35$ ,  $p=0.0001$ ). The mean CIMT of hypertensive case and the control was  $0.76 \pm 0.27$  mm and  $0.62 \pm 0.18$  mm, ( $z=3.87$ ,  $p=0.0001$ ). The mean CIMT of alcoholic case and the control was  $0.73 \pm 0.26$  mm and  $0.64 \pm 0.24$  mm, ( $z=1.35$ ,  $p=0.180$ ). The mean CIMT of smoker and nonsmoker was  $0.83 \pm 0.28$  mm and  $0.62 \pm 0.14$  mm ( $z=3.80$ ,  $p=0.0001$ ).

Similar result was found in the study of Arun Kumar et al., [27] showing mean CIMT in diabetic patients as 0.89 mm compared to non-diabetics 0.78 mm ( $p<0.001$ ). The mean CIMT in these subjects was 0.87 mm higher than non-smokers 0.82 mm ( $p=0.04$ ). The mean CIMT was higher in hypertensive group 0.87 mm, the p-value being  $<0.001$ .

In present study, On multiple regression analysis it was found that CIMT and other risk factor like age, gender and DM are independent variables ( $p=0.008$ ,  $p=0.030$  and  $p=0.0001$  respectively) and other risk factors like HTN, alcohol, smokers and dyslipidemia are dependent to each other. Nakashima, Yorioka et al., [23] also found the independent risk factor associated with maximum CIMT value were age, diabetes mellitus and smoking ( $p<0.0001$ ).

## Conclusion

In this study even though CIMT was marginally more in the late stages of CKD patients, no statistically significant correlation was found between them. It was also found that CIMT and other risk factor like Age, gender and DM were independent variables and other risk factors like HTN, alcohol, smokers and dyslipidemia were dependent to each other.

## Conflict of Interest

All authors disclose that there was no conflict of interest.

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