ORIGINAL RESEARCH PAPER

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KEY WORDS:

ASSOCIATION OF CAROTID INTIMAL MEDIAL THICKNESS IN PATIENTS FOR CARDIOVASCULAR DISEASE LIKE ISCHEMIC HEART DISEASE IN CHRONIC KIDNEY PATIENTS

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INTRODUCTION

Chronic Kidney Disease (CKD) is a very serious complication equated with very early death and quality of life is decreased in such patients. Because of this there could be huge increase in health care expenditures.[1,2,3] The overall prevalence of renal stage disease in the end stage may continue to rise globally. Moreover, if we see the current patterns the number of patients with early CKD (chronic kidney disease) from which end stage renal disease may develop in the future may emerge leading to the present status of increasing number of end- stage renal disease by a factor of 30 to 60.[4,5] The overt disease morbidity of chronic kidney disease (CKD) in our country cannot be determined accurately. The approximate number of overall cases of CKD ranges from about eight hundred per million population and the new cases among the end-stage renal disease (ESRD) is about one hundred fifty to two hundred per million population.[6] More over early CKD (Chronic kidney disease) will not progress to later stage which is end-stage renal disease in all patients. But there are instances where many will probably die of conditions associated with them. So many patients with CKD (Chronic Kidney Disease) have cardiovascular disease and die prematurely from this condition instead of surviving long enough to face dialysis or transplantation.[7,8] Different surveys showed that the risk factor for certain cardiovascular disease may increase much earlier in chronic kidney disease and in cases of renal dysfunction also, even at higher glomerular filtration rates.[1,9] More over people with chronic kidney disease may have a tendency of excess traditional risk factors for cardiovascular disease such as hypertension, diabetes, and hyperlipidemias.[7] Renal disease also endangers the environment which promotes cardiovascular injury in a ways which is more or less specific to end-stage renal disease. Vascular calcification can happen with dysregulation of calcium and phosphorus among the usually liable individuals of end-stage renal disease.[10,11,12] Most of the evidence shows that the nature of the vascular disease associated with end-stage renal disease may evolve over in patients with progressive renal impairment and it may co-relate with standard risk factors like diabetes, dyslipidemia and hypertension. Hence, this study mainly concentrates on the relation of carotid intimal thickness in different stages of chronic kidney disease. Atherosclerosis as it says, is a severe form which is often asymptomatic, as it involves a direct identification of vessel wall which is necessary to detect affected individuals at an early stage. However, it is suggested by the IAP (International Atherosclerosis Project) that it is a process which occurs simultaneously in the carotid, cerebral and coronary arteries.[11] Carotid artery IMT (Intimal medial thickness) is well-established index of systemic atherosclerosis which co-relate well with the incidence of coronary heart disease as well as stroke.[12,13] The same index correlates well with uremic population as well as non-uremic population.[14] It is shown that carotid artery intimal medial thickness acts an independent predictor of mortality of cardiovascular risk factor among patients who are undergoing hemodialysis.[15,16] The measurement of CIMT (carotid artery intimal medial thickness) of the common carotid artery by B-Mode ultrasound was significantly found to have suitable noninvasive method to visualize the arterial walls and to determine the early stages of the process of atherosclerosis.[17-20] Carotid artery intimal medial thickness when it is measured is very helpful in making the correct decision as to which is the best method of treatment, either surgical or medical in patients with carotid artery stenosis and it is also helpful in assessing the effects of medical therapies of atherosclerosis.[19] CKD is characterized by a gradual decrease in glomerular filtration rate and past evidence of population of nephron.[20]

The course is substantially one of the most progressive and leading to the loss of nephron function indicating a end-stage renal disease. Kidney failure is the most vital aspect of the spectrum, which indirectly represent a minority of the entire population being affected by kidney disease.There is always a time gap between the initial onset of disease and development of end-stage renal disease which may considerably vary not only with similar disease processes but also at different disease stages.The long progressive nature of the patients with chronic kidney disease and the ensuing end-stage renal disease is making it a substantial additional burden on entire health resources since all other modalities of procedures are expensive. There are various factors for kidney injury which may lead to the final common pathway of end-stage renal disease and this syndrome is characterized by metabolic disorders such as hypertension, anemia, renal bone disease , malnutrition, neuropathy and quality of life being impaired and reduced expectancy of life. There are much increased evidence acquired in the past decades where there are much adverse outcomes of chronic kidney disease such as renal failure,cardiovascular disease and premature death which can be easily prevented by delay in detection of chronic kidney diseases.Initial stages of chronic kidney disease can be evaluated through laboratory investigations tests alone. Treating the earlier stages of chronic kidney disease and initiating the treatment of cardiovascular risk factors at early stage of chronic kidney disease should be very effective in reducing the rate of progression to end-stage renal disease.Among patients with chronic kidney disease, the atherosclerotic cardiovascular disease may be leading cause for disease burden and death. The carotid artery intimal medial thickness has been involved as a marker for diagnosing early atherosclerosis. The overall increased incidence of cardiovascular disease are the consequences of a high prevalence of both traditional risk factors, uremia-related "new factors" and additional oxidative stress can very well lead to increase in atherosclerotic risk among the patients. With respect to National Health and Nutrition Examination Survey (NHANES), the overall prevalence of chronic kidney disease among the Unites states of America population is fifteen percentages. It becomes apparent that the severity of chronic kidney disease along with the cardiovascular disorder in any large population make is very vulnerable combination for both patients and healthcare systems.On an average fifty percent of patients with end stage renal disease will die from a cardiovascular incidence where it is indicative of a cardiovascular mortality that is thirty times higher among patients undergoing dialysis and five hundred times higher in the age group of twenty-five- to thirty-four-year-old end stage renal disease patients than in individuals

from the general population of the same age and race.There are many previous studies suggesting that CIMT i.e., carotid artery intimal medial thickness can be used as a marker for atherosclerosis cardiovascular disease. Non invasive assessment of intima medial thickness of carotid arteries by high resolution B – mode ultrasonography is widely used in observational studies and trials as an intermediate or proxy measure of generalized atherosclerosis. Increased intima medial thickness of carotid arteries has been associated with unfavorable levels of established cardiovascular risk factors, prevalent cardiovascular disease and atherosclerosis elsewhere in the arterial system.Individuals with lesser degrees of renal dysfunction are also predisposed to cardiovascular events. Several recent reports from prospective population-based studies suggest that mild-to-moderate renal insufficiency predicts cardiovascular morbidity and mortality. Indeed, patients with CKD are more likely to die of CVD than to develop renal failure. In patients with CKD there is a high prevalence of traditional CVD risk factors,such as diabetes, hyperlipidemia and hypertension. Some studies, however, indicate that the relationships between estimated glomerular filtration rate (eGFR) and CVD morbidity, and mortality are independent of these characteristics.These observations have led to the suggestion that "nontraditional" risk factors such as inflammation, abnormal calcium and phosphorous metabolism, anemia, hyperparathyroidism, hypoalbuminemia and anemia may contribute to the risk of CVD in CKD patients.

MATERIALS AND METHODS

Single centre, Prospective study,Over One year and six months was conducted among the patients in the Department of Nephrology, D Y Patil hospital, Navi Mumbai.Chronic kidney disease patients on conservative as well as on maintenance hemodialysis were the target population.The 100 patients age greater than 18 years who fulfilled the KDIGO definition for CKD on conservative management as well as those on dialysis were taken into the study with stage 3, and 4, 5.Routine investigations like CBC, RBS, RFT, Urine Routine and microscopy, LFT, Lipid profile, etc.GFR was calculated on the basis of age, gender, serum creatinine by computer generated CKD EPI equation.All patients of chronic kidney disease were subjected for high resolution B - mode Carotid Doppler ultrasound done by the same senior radiologist to rule out inter personal variation. Bilateral assessment of intimal thickness was done in common carotid artery and higher CIMT value of any of the carotid artery was taken.

RESULTS

Mean And Standard Deviations

Lab parameters	Mean±SD
Age	56.34 ± 13.79
Sr. Creatinine	5.76 ± 3.3
BUN	49.62 ± 21.8
Urea	101.27 ± 45.42
Proteinuria	974.1 ± 579.48
Total Proteins	6.79 ± 0.3
Sr. Albumin	3.65 ± 0.4
Haemoglobin	10.73 ± 2.57
Sr. Calcium	8.04 ± 0.8
Sr. Phosphorous	4.96 ± 1.2
25 OH vitamin D	20.56 ± 5.4
Sr. PTH	450.29 ± 146.6
Total Cholesterol	202.66 ± 43.39
LDL	105.34 ± 36.65
TG	197.05 ± 74.97
HDL	42.49 ± 9.38
CIMT at start of study	0.91 ± 0.23
CIMT at end of study	0.91 ± 0.23

In our study, the mean ± SD age is 56.34 ± 13.79, mean ± SD Sr. Creatinine is 5.76 ± 3.3, mean ± SD blood urea nitrogen is 49.62 ± 21.8, mean ± SD urea levels are 101.27 ± 45.42, mean ± SD proteinuria is 974.1 ± 579.48, mean ± SD total proteins levels is 6.79 ± 0.3, mean ± SD serum albumin levels are 3.65 ± 0.4, mean ± SD hemoglobin levels are 10.73 ± 2.57, mean ± SD serum calcium levels are 8.04 ± 0.8, mean ± SD serum phosphorous levels are 4.96 ± 1.2, mean ± SD 25 OH vitamin D levels are 20.56 ± 5.4, mean ± SD PTH levels are 450.29 ± 146.6, mean ± SD total cholesterol levels are 202.66 ± 43.39, mean ± SD LDL levels are 105.34 ± 36.65, mean ± SD triglyceride levels are 197.05 ± 74.97, mean ± SD HDL levels are 42.49 ± 9.38, mean ± SD CIMT at the start of the study is 0.91 ± 0.23, mean ± SD CIMT at the end of the study is 0.91 ± 0.23.

Distribution Of Study Participants According To Their Presence Of Cardiovascular Risk Factor (n=100)

Cardiovascular risk factor	patients (Out of 100)
Hyperparathyroidism	93
Hypertension	83
Diabetes Mellitus	52
Hyperlipidemia	51
Obesity	38

Hyperparathyroidism was the most common cardio vascular risk factor present among 93% of patient. Hypertension was the second most common cardio vascular risk factor present among 83% of patients, followed by diabetes mellitus present in among 52% of patients followed by hyperlipidemia which was present among 51% of the study participants, followed by obesity accounting for 38%.

In our study, 10% patients belonged to KDIGO CKD stage 3, 30% patients belonged to KDIGO CKD stage 4, 30% patients belonged to KDIGO CKD stage 5 and 30% patients belonged to KDIGO CKD stage 5d. Out of 10 patients in stage 3 CKD, 9 patients had CIMT < 0.89 and 1 patient had CIMT > 0.89, out of 30 patients in stage 4 CKD, 12 patients had CIMT < 0.89 and 18 patients had CIMT > 0.89, out of 30 patients in stage 5 CKD, 14 patients had CIMT < 0.89 and 16 patients had CIMT > 0.89, out of 30 patients in CKD stage 5d, 11 patients had CIMT < 0.89 and 19 patients had CIMT > 0.89. When chi square test was applied to the data P Value was 0.02 which is statistically significant.

CKD stage** CIMT Score			
CKD stage	<0.89	>0.89	Total
3	9	1	10
4	12	18	30
5	14	16	30
5d	11	19	30
Total	46	54	100

In our study, mean ± SD CIMT for CKD stage 3 is 0.78 ± 0.19, mean ± SD CIMT for CKD stage 4 is 0.92 ± 0.23, mean ± SD CIMT for CKD stage 5 is 0.92 ± 0.21 and mean ± SD CIMT for CKD stage 5d is 0.95 ± 0.24.

CKD stage	Mean ± SD CIMT
3	0.78 ± 0.19
4	0.92 ± 0.23
5	0.92 ± 0.21
5d	0.95 ± 0.24

In our study to study the association of carotid intimal medial thickness and for cardio-vascular disease we collected data for patients suffering acute myocardial infarction, heart failure, acute Ischemic stroke, peripheral vascular disease during the one-year study period.

Out of 100 patients, 23 patients suffered from heart disease, amongst which 20 patients had CIMT on the higher side which is CIMT > 0.89 and 3 patients had CIMT less then <0.89. When Chi square test was applied to this data, the P Value came out to be 0.0003233324, which is statistically significant.

	CIMT Score	CIMT Score

Heart disease	>0.89	<0.89	Total
Yes	20	3	23
No	34	43	77
Total	54	46	100

Out of 100 patients, 6 patients suffered from acute ischemic CVA, amongst which all 6 patients had CIMT on the higher side which is CIMT > 0.89. When Chi square test was applied to this data, the P Value came out to be 0.020, which is statistically significant.

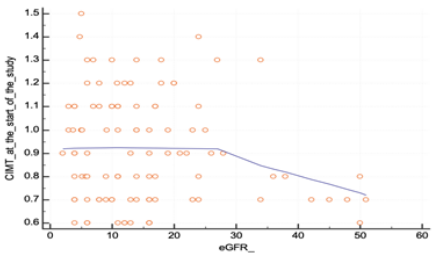
	CIMT Score		CIMT Score
Ischemic CVA	>0.89	<0.89	Total
Yes	6	0	6
No	48	46	94
Total	54	46	100

Out of 100 patients, 14 patients suffered from peripheral vascular disease in the form of non-healing ulcers, amputations, etc. amongst which 12 patients had CIMT on the higher side which is CIMT > 0.89 and 2 patients had CIMT < 0.89. When Chi square test was applied to this data, the P Value came out to be 0.0106, which is statistically significant

	CIMT Score		
PVD	>0.89	<0.89	Total
Yes	12	2	14
No	42	44	86
Total	54	46	100

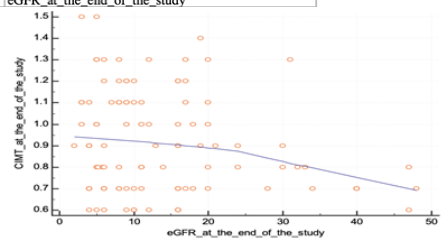
Sample size	100
Spearman's coefficient of rank correlation (rho)	-0.0939
Significance level	P=0.3526
95% Confidence Interval for rho	-0.285 to 0.104

Variable Y	CIMT_at_the_start_of_the_study
Variable X	eGFR_



Sample size	100
Spearman's coefficient of rank correlation (rho)	-0.150
Significance level	P=0.1356
95% Confidence Interval for rho	-0.337 to 0.0475

Variable Y	CIMT_at_the_end_of_the_study
Variable X	eGFR_at_the_end_of_the_study



When review doppler was done at the end of the study and CIMT was compared at the start and end of the study with the corresponding eGFR at the start and end of the study, there was a negative corelation seen in bothe scenarios indicating declining GFR with increasing CIMT values.

Out of 100 people, 83 patients had hypertension, which was the second most common cardio vascular risk factor, out of 83 patients, 46 patients had higher CIMT i.e.> 0.89 and 37 patients had CIMT < 0.89. When Chi square test was applied to the data, P value came out to be 0.530 which is staistically not significant.

	CIMT L/H		
HTN	> 0.89	< 0.89	Total
Yes	46	37	83
No	8	9	17
Total	54	46	100

In our study population, out of 100 people, 52 patients had Diabetes Mellitus, which was the third most the common cardio vascular risk factor, out of 52 patients, 35 patients had CIMT > 0.89 and 17 patients had CIMT < 0.89. When Chi square test was applied to the data, P value came out to be 0.005 which is staistically significant.

DISCUSSION

In our study a total of one hundred patients were studied for CIMT in association with cardiovascular risk and risk factors. Mean age of the patients were 56.34 ± 13.79 years. In the current study the mean carotid artery intimal medial thickness in chronic kidney disease patients was 0.91 ± 0.23which is comparable with other studies done by Shoji et al [21] who studied carotid artery intimal medial thickness in one hundred and ten pre-dialysis patients with 0.88± 9 0.03 mm. The present study showed strong association between CIMT and history of hyperlipidemia (p=0.46) similar results were obtained in a study by Brzosko et al [22](P = 0.02).The mean hemoglobin level in the study population was 10.73 ± 2.57 g/dl. There is no significant correlation between hemoglobin levels+ serum albumin levels with CIMT, but in other studies there was significant correlation.[23,24]In the present study there was significant correlation of serum cholesterol with CIMT. Attman et al[25] in their study showed no significant change in levels of total cholesterol. Similar results were obtained in study by Kawagishi[26] et.al. Thomas Quasctining et al[27] reported combined hyperlipidemia (elevated total cholesterol and triglycerides) in their study.In the present study there was significant correlation of diabetic status and with CIMT. Findings are similar to study done by Katarzyna Janda et al . & in study by R R Kasliwal [28] et.al. In the present study there was no significant association of hypertension and no significant association of secondary hyperparathyroidism of chronic kidney disease with CIMT. However other studies did show significant association of presence of hypertension with higher CIMT values such as one done by R R Kasliwal 28 et.al. However a study done by Dos santos VM et al [29] did show significant association of presence of obesity with higher CIMT values in chronic kidney disease.In the present study there was a significant association with increasing CIMT values with worsening of GFR and or increasing stages of CKD, however this is in contrast to study done by Chhajed et al[30] and also a study done by V Margekar et al [31] where they did not show significant association of higher CIMT values with increasing stages of KDIGO chronic kidney disease classes. In the present study there was a significant association of higher CIMT values i.e. CIMT >0.89 with higher risk for cardio vascular diseases such as Ischemic heart disease, ischemic stroke, peripheral vascular disease. This is in similar to findings of a study done by Tejaswini et al and Nagesh et al [32].

CONCLUSION

CIMT has been shown to correlate with cardiac risk factors, to be an independent predictor of future myocardial infarction and stroke risk along with the traditional risk factors such as Diabetes, hypertension, hyperlipidemia, obesity, etc. The measurement of CIMT (carotid artery intimal medial thickness) of the common carotid artery by B-Mode ultrasound was significantly found to have suitable noninvasive method to visualize the arterial walls and to determine the early stages of the process of atherosclerosis. In patients with CKD with multiple risk factors for cardiovascular disease have more carotid intimal medial thickness than chronic kidney disease with one or two risk factors for cardiovascular disease.

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