CORRELATION OF CAROTID INTIMAL-MEDIAL THICKNESS WITH ESTIMATED GLOMERULAR FILTRATION RATE AND CARDIOVASCULAR RISK FACTORS IN PATIENTS OF CHRONIC KIDNEY DISEASE

Tejinder Sikri¹, Ramesh Chander², Pashaura Singh³, Sunil Kumar⁴, Kashmir Singh⁵, Saurabh Agarwal⁶, Pankaj Kumar⁷, Jagbir Singh⁸

¹Professor, Department of Medicine, Government Medical College, Amritsar.

²Associate Professor, Department of Radio-Diagnosis, Government Medical College, Amritsar.

³Assistant Professor, Department of Medicine, Government Medical College, Amritsar.

⁴Junior Resident, Department of Medicine, Government Medical College, Amritsar.

⁵Senior Resident, Department of Medicine, Government Medical College, Amritsar.

⁶Junior Resident, Department of Medicine, Government Medical College, Amritsar.

⁷Junior Resident, Department of Medicine, Government Medical College, Amritsar.

⁸Junior Resident, Department of Medicine, Government Medical College, Amritsar.

ABSTRACT

BACKGROUND

Chronic Kidney Disease (CKD) is associated with premature mortality, decreased quality of life and increased health care expenditures.^{1,2} Many patients with CKD have cardiovascular disease and die prematurely from this condition instead of surviving long enough to face dialysis or transplantation.^{3,4} Carotid Intimal-Medial Thickness (CIMT) predicts future vascular events in the general population. However, the correlation of traditional cardiovascular risk factors and estimated glomerular filtration rate in Chronic Kidney Disease (CKD) with CIMT is not studied extensively. To determine the correlation of CIMT with traditional cardiovascular risk factors like age, Body Mass Index (BMI), dyslipidaemia and estimated glomerular filtration of CKD patients, CIMT was measured by means of high-resolution B-mode ultrasonography.

MATERIALS AND METHODS

In this randomised open study, in which 70 patients with chronic kidney disease at the Medicine/Nephrology Inpatients/Outpatients Department of the Guru Nanak Dev Hospital, Amritsar and 30 age and sex matched controls were enrolled. Data needed for the study was extracted from the files of patients. Estimated glomerular filtration rate was calculated by using Cockcroft-Gault (CG) formula. CIMT was measured using B-mode ultrasound.

RESULTS

- In our study, we found that CIMT in selected patients correlated significantly with traditional cardiovascular risk factors like age ($r=0.377$, p -value = 0.00), systolic blood pressure ($r=0.517$, p -value = 0.00), diastolic blood pressure ($r=0.487$, p -value = 0.00), BMI ($r=0.223$, p -value = 0.026), total cholesterol ($r=0.482$, p -value = 0.00), LDL cholesterol ($r=0.210$, p -value = 0.036), serum triglycerides ($r = 0.636$, p -value = 0.00), HDL cholesterol ($r = -0.480$, p -value = 0.00).
- Mean CIMT of smokers, diabetic was significantly higher as compared to non-smokers, non-diabetic patients and statistically significant (t -value = 2.53, p -value = 0.01), (t -value = -0.592, p -value = 0.557) respectively.
- Mean CIMT of CKD patients was (0.87 ± 0.09) and healthy volunteers was (0.63 ± 0.08). We further observed that CIMT in selected patients showed significant negative correlation with estimated glomerular filtration rate ($r = -0.761$, p -value = 0.00).

CONCLUSION

Therefore, it can be concluded that CIMT measurement by B-mode ultrasonography seems to be of clinical value in screening of CKD patients as an early marker of advanced atherosclerosis. Increased CIMT as an indicator of subclinical cardiovascular disease may help to identify such patients, who would benefit from aggressive therapeutic measures.

KEYWORDS

CIMT, CKD, Atherosclerosis, eGFR, Cardiovascular Disease.

HOW TO CITE THIS ARTICLE: Sikri T, Chander R, Singh P, et al. Correlation of carotid intimal-medial thickness with estimated glomerular filtration rate and cardiovascular risk factors in patients of chronic kidney disease. J. Evolution Med. Dent. Sci. 2017;6(3):202-206, DOI: 10.14260/Jemds/2017/47

Financial or Other, Competing Interest: None.

Submission 01-12-2016, Peer Review 28-12-2016,

Acceptance 04-01-2017, Published 09-01-2017.

Corresponding Author:

Dr. Sunil Kumar,

H. No. F-13/446,

Nehru Colony,

Gopal Nagar,

Amritsar, Punjab.

E-mail: sunilbamel1988@gmail.com

DOI: 10.14260/Jemds/2017/47

BACKGROUND

Chronic Kidney Disease (CKD) is a devastating disease with clinical, economic and ethical dimensions, and is a recently recognised major public health problem.⁵ Recent independent studies identified the decline of renal function in patients as an independent predictor of all-cause mortality as well as adverse Cardiovascular Disease (CVD) events. In a community-based population with pre-existing cardiovascular disease, the presence of chronic kidney disease (Defined as an Estimated Glomerular Filtration Rate (eGFR) of less than 60 mL/min/1.73 m²) has been associated

with an increased risk of recurrent cardiovascular disease outcomes after adjustment for traditional cardiovascular disease risk factors.^{6,7}

Some authors demonstrated that increased Carotid Intima-Medial Thickness (CIMT), which is clinically considered as the surrogate endpoint of cardiovascular disease which occurs early in the course of chronic kidney disease.^{8,9} These changes are associated with higher cardiovascular disease risk factors in patients with chronic kidney disease.^{10,11} Limited information is available on whether or not the decline in renal function is an independent risk factor for cardiovascular disease. The present study was undertaken to evaluate the same.

MATERIALS AND METHODS

In this randomised open study, in which 70 patients with chronic kidney disease at the Medicine/Nephrology Inpatients/Outpatients Department of the Guru Nanak Dev Hospital, Amritsar, and 30 age and sex matched controls were enrolled. Patients of acute renal failure, history of carotid surgery, age less than 18 years, those who were on hypolipidaemic drugs and patients having a previous history of ischaemic heart disease. Detailed history was taken and thorough general and systemic examination was done. Physical examination included height and weight measurements for calculating Body Surface Area (BSA). Routine baseline investigations were performed, i.e. Hb, TLC, DLC, PBF, ESR, Blood Urea and Serum Creatinine and Lipid Profile. Estimated Glomerular Filtration Rate (eGFR) was calculated by using Cockcroft-Gault (CG) formula using creatinine clearance (CrCl).

Carotid Doppler ultrasonography was performed by a single operator and the CIMT was measured using B-mode ultrasound and a 7.5 MHz transducer. Intimal-medial thickness was defined as the distance between the leading edge of the first echogenic line (Lumen-intima interface) and the second echogenic line (Media-adventitia interface) of the far wall over the area devoid of atherosclerotic plaque.^{12,13} Three measurements were taken at 0.5, 1 and 2 cm below the carotid bifurcation of the common carotid artery on each side and their arithmetic averages were calculated. The intimal-medial thickness of both sides (right and left) was also calculated and the average of these two values was

calculated. In this study, an atherosclerotic plaque is defined as a local thickness of intima greater than 1 mm or two times more than its adjacent normal layer.

Statistical Analysis

The statistical software SPSS Ver. 21 was used for statistical analysis. The mean $\pm$ standard deviation was calculated. Pair-wise comparison between the cases and controls was performed for all parameters using student's unpaired t-test. The values of $P < 0.05$ were considered as significant. Bivariate correlation analysis was used to see the correlation of different variables with CIMT.

RESULTS

A total of 70 CKD patients (32 males and 38 females) were enrolled in the study in Group A and 30 healthy volunteers (18 males and 12 females) were enrolled in the study in Group B. Mean age of Group A and Group B were 53.25 ± 16.47 and 38.86 ± 18.26 , respectively. In our study, we found that CIMT in selected patients correlated significantly with traditional cardiovascular risk factors like age ($r=0.377$, p -value = 0.00), systolic blood pressure ($r=0.517$, p -value = 0.00), diastolic blood pressure ($r = 0.487$, p -value = 0.00), BMI ($r= 0.223$, p -value = 0.026), total cholesterol ($r = 0.482$, p -value = 0.00), LDL cholesterol ($r = 0.210$, p -value = 0.036), serum triglycerides ($r=0.636$, p -value= 0.00), HDL cholesterol ($r = -0.480$, p -value = 0.00).

In our study, it was observed that there was statistically significant difference of CIMT between diabetic and non-diabetic patient (t -value = -0.592, p -value = 0.557). Mean CIMT of smokers was significantly higher as compared to non-smokers and statistically significant (t -value = 2.53, p -value = 0.01).

Mean eGFR of Group A was (16.9 ± 7.8) and Group B was (112.22 ± 29.2) and there was statistically significant difference of eGFR distribution between the two groups (t -value = 25.3, p -value = 0.00). Mean CIMT of Group A was (0.87 ± 0.09) and Group B was (0.63 ± 0.08) and that there was statistically significant difference of CIMT distribution between the two groups (t -value = -11.3, p -value = 0.00).

In our study, we further observed that CIMT in selected patients showed significant negative correlation with estimated glomerular filtration rate ($r=-0.761$, p -value = 0.00).

Sl. No.	Variable	Mean of Group A (N = 70)	Mean of Group B (N = 30)	t-value	p-value
1	Age (Years)	53.25 ± 16.47	49.13 ± 14.3	1.19	0.237
2	BMI (kg/m^2)	28.1 ± 4.25	24.17 ± 2.96	-4.58	0.00
3	Systolic BP (mmHg)	154.3 ± 18.5	118.1 ± 7.5	-10.3	0.00
4	Diastolic BP (mmHg)	102.7 ± 14.8	79.0 ± 6.8	-8.35	0.00
5	Serum TC (mg/dL)	243.2 ± 37.7	187.4 ± 11.6	-7.92	0.00
6	LDL (mg/dL)	133.2 ± 29.9	115.0 ± 8.3	-3.21	0.002
7	HDL (mg/dL)	41.3 ± 4.0	49.1 ± 5.4	7.907	0.00
8	Serum Triglycerides (mg/dL)	343.7 ± 98.0	114.5 ± 18.1	-12.6	0.00
9	eGFR	16.9 ± 7.8	112.2 ± 29.2	25.3	0.00
10	CIMT (mm)	0.87 ± 0.09	0.63 ± 0.08	-11.3	0.00

Table 1. Comparison of Means of CKD Patients (Group A) and Healthy Volunteers (Group B)

Sl. No.	Correlation of Variables with CIMT	Correlation Coefficient (r value)	p-value
1	Age with CIMT	0.377	0.00
2	BMI with CIMT	0.223	0.026
3	SBP with CIMT	0.517	0.00
4	DBP with CIMT	0.487	0.00
5	TC with CIMT	0.482	0.00
6	LDL with CIMT	0.210	0.036
7	HDL with CIMT	-0.480	0.00
8	TG with CIMT	0.636	0.00
9	eGFR with CIMT	-0.761	0.00

Table 2. Comparison of Different Variables with CIMT

Figure 1. Comparison of CIMT of CKD Patients and Healthy Controls

Figure 2. Comparison of CIMT between Diabetic and Non-Diabetic CKD Patients

Figure 3. Comparison of CIMT between Smoker and Non-Smoker CKD Patients

DISCUSSION

Some authors demonstrated that increased Carotid Intima-Medial Thickness (CIMT), which is clinically considered as the surrogate endpoint of cardiovascular disease, occurs early in

the course of chronic kidney disease.^{8,9} These changes are associated with higher cardiovascular disease risk factors in patients with chronic kidney disease.^{10,11} Limited information is available on whether or not the decline in renal function is an independent risk factor for cardiovascular disease. The present study was undertaken to evaluate the same.

In our study, we found that CIMT in selected patients correlated significantly with traditional cardiovascular risk factors like age ($r = 0.377$, $p\text{-value} = 0.00$), systolic blood pressure ($r = 0.517$, $p\text{-value} = 0.00$), diastolic blood pressure ($r = 0.487$, $p\text{-value} = 0.00$). Study by Takato et al showed similar results for risk factors age and diabetes.¹⁴ Yilmaz et al in their study observed that IMT was independently associated with CKD stage and mean arterial pressure.¹⁵ Ekart et al found a statistically significant correlation between carotid IMT and the average one-monthly diastolic BP ($P < 0.05$) and ambulatory BP monitoring ($P < 0.05$).¹⁶

In our study, we found that CIMT in selected patients correlated significantly with BMI ($r = 0.223$, $p\text{-value} = 0.026$), total cholesterol ($r = 0.482$, $p\text{-value} = 0.00$), LDL cholesterol ($r = 0.210$, $p\text{-value} = 0.036$), HDL cholesterol ($r = -0.480$, $p\text{-value} = 0.00$), serum triglycerides ($r = 0.636$, $p\text{-value} = 0.00$). Similar results were observed by Szeto et al.¹⁷

In our study, it was observed that there was statistically significant difference of CIMT between diabetic and non-diabetic patient ($t\text{-value} = -0.592$, $p\text{-value} = 0.557$). Study by Takato et al showed similar results for risk factors age and diabetes.¹⁴ Above mentioned findings were consistent with observations of Kawamoto et al.¹⁸ Similar observations were made by Szeto et al,¹⁷ carotid IMT was significantly higher in patients with diabetes than in those without diabetes (0.930 ± 0.254 versus 0.794 ± 0.184 ; $P = 0.002$).

Mean of CIMT of smokers was significantly higher as compared to non-smokers and statistically significant ($t\text{-value} = 2.53$, $p\text{-value} = 0.01$). Similar results were shown by multiple regression analysis by Kawamoto et al, smoking status was significantly associated with CIMT.¹⁹

Mean CIMT of Group A was (0.87 ± 0.09) and Group B was (0.63 ± 0.08) and that there was statistically significant difference of CIMT distribution between the two groups ($t\text{-value} = -11.3$, $p\text{-value} = 0.00$).

In our study, we further observed that CIMT in selected patients showed significant negative correlation with estimated glomerular filtration rate ($r = -0.761$, $p\text{-value} = 0.00$).

In another study, similar observations were made. Stepwise multiple linear regression analysis using IMT as an objective variable, adjusted by various factors as explanatory variables showed that eGFR was a significant independent contributing factor along with known risk factors in men (β , -0.096 ; $p = 0.018$) and women (β , -0.080 ; $p = 0.035$).¹⁸ Similar results were also found in another study.²⁰

The reasons for the high CVD 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. Such factors include uric acid, homocysteine, C-reactive protein, albuminuria, oxidative stress, endothelial dysfunction and cytokines.²¹⁻²⁶

Chronic kidney disease may be complicated by both duration and severity of other causes of CVD and exacerbate atherosclerosis caused by CVD risk factors. The duration of

exposure to adverse CVD risk factors may be the largest in patients with pronounced CKD.

SUMMARY AND CONCLUSION

In this present study in which 70 patients with chronic kidney disease and 30 age and sex matched controls were enrolled.

In each patient, a detailed history, physical examination, laboratory evaluation and CIMT were recorded as per the proforma.

The Observations of this Study are Summarised as follows -

- Mean of Age, BMI, systolic blood pressure, diastolic blood pressure, total cholesterol, LDL cholesterol, VLDL cholesterol, serum triglycerides was significantly higher in CKD patients (Group A) as compared to healthy volunteers (Group B).
- Mean of HDL cholesterol was statistically significant lower in CKD patients as compared to control group.
- Mean of eGFR was also statistically significant lower in CKD patients as compared to control group.
- Mean CIMT was also statistically significant, higher in CKD patients as compared to control group.
- Mean CIMT was also statistically significant, higher in diabetic patients as compared to non-diabetics.
- Mean CIMT was also statistically significant, higher in smokers as compared to non-smokers.
- CIMT in selected patients showed statistically significant positive correlation with traditional cardiovascular risk factors like age, BMI, systolic blood pressure, diastolic blood pressure, total cholesterol, LDL cholesterol, VLDL cholesterol and serum triglycerides.
- CIMT in selected patients showed statistically significant negative correlation with HDL cholesterol and eGFR.

Therefore, it can be concluded that CIMT measurement by B-mode ultrasonography seems to be of clinical value in screening of CKD patients as an early marker of advanced atherosclerosis. Increased CIMT as an indicator of subclinical cardiovascular disease may help to identify such patients, who would benefit from aggressive therapeutic measures.

Acknowledgement

At the outset, I endow my sincere thanks to my supervisor, my mentor and my guide, Dr. Tejinder Sikri, MD, Professor, Department of Medicine, Government Medical College. This work could not have been possible without his immense efforts and guidance. I am grateful to him for his astute guidance that helped me to become a good clinician and above all a good human being.

At this stage, I would like to express my sincere gratitude to my Co-Supervisor, Dr. Ramesh Chander, MD, Associate Professor, Department of Radiodiagnosis, Government Medical College, Amritsar for his continuous support towards the study and research. I am indebted to Sir for his patience, support and enthusiasm for the Research work.

I am thankful to my Seniors, Colleagues and Juniors of Department of Medicine, Government Medical College, Amritsar without whose willing and wholehearted cooperation and optimistic and loving attitude it would have been impossible to complete this work the way it has been.

To my parents, Mr. Ranvir Singh and Mrs. Usha Rani and my younger brother Bhumi and my sister Sangeet, I owe a special reverence for their unending and unconditional support, encouragement and blessings at every step of my life. It is a pleasure to thank my friends for their love and encouragement.

My words are not sufficient to express my gratitude to all my patients who peep behind every typed word of this project and without whose cooperation this project would not have seen the light of the day.

REFERENCES

- [1] Go AS, Chertow GM, Fan D, et al. Chronic kidney diseases and the risk of death, cardiovascular events, and hospitalization. *N Eng J Med* 2004;351(13):1296-305.
- [2] Briet M, Bozec E, Laurent S, et al. Arterial stiffness and enlargement in mild-to-moderate chronic kidney disease. *Kidney Int* 2006;69(2):350-7.
- [3] Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American heart association councils on kidney in cardiovascular disease, high blood pressure research, clinical cardiology, and epidemiology and prevention. *Circulation* 2003;42(5):1050-65.
- [4] Goodman WG, London G, Amann K, et al. Vascular calcification in chronic kidney disease. *Am J Kidney Dis* 2004;43(3):572-9.
- [5] Nitesh C, Subhash CBJ, Manjunath SS, et al. Correlation of carotid intimal-medial thickness with estimated glomerular filtration rate and cardiovascular risk factors in chronic kidney disease. *Saudi Journal of Kidney Disease and Plantation* 2014;25(3):572-6.
- [6] Shoji T, Emoto M, Tabata T, et al. Advanced atherosclerosis in predialysis patients with chronic renal failure. *Kidney Int* 2002;61(6):2187-92.
- [7] Preston E, Ellis MR, Kulinskaya E, et al. Association between carotid artery intima-media thickness and cardiovascular risk factors in CKD. *Am J Kidney Dis* 2005;46(5):856-62.
- [8] Zhang L, Zhao F, Yang Y, et al. Association between carotid artery intima-media thickness and early-stage CKD in a Chinese population. *Am J Kidney Dis* 2007;49(6):786-92.
- [9] Taniwaki H, Kawagishi T, Emoto M. Correlation between the intima-media thickness of the carotid artery and aortic pulse-wave velocity in patients with type 2 diabetes. *Vessel wall properties in type 2 diabetes. Diabetes Care* 1999;22(11):1851-7.
- [10] Zoccali C, Benedetto FA, Maas R. Asymmetric dimethylarginine, C-reactive protein, and carotid intima-media thickness in end-stage renal disease. *J Am Soc Nephrol* 2002;13(2):490-6.
- [11] Malatino LS, Mallamaci F, Benedetto FA, et al. Hepatocyte growth factor predicts survival and relates to inflammation and intima media thickness in end-stage renal disease. *Am J Kidney Dis* 2000;36(5):945-52.
- [12] Kawagishi T, Nishizawa Y, Konishi T, et al. High resolution B-Mode ultra sonography in evaluation of atherosclerosis. *N Engl J Med* 1974;200:697-701.

- [13] Poyrazoglu HM, Dusunsal R, Yikilmaz A, et al. Carotid artery thickness in children and young adult with ESRD. *Pediatr Nephrol* 2007;22(1):109-16.
- [14] Takato T, Yamada N, Ashida T. Effects of aging and sex on progression of carotid intima-media thickness: a retrospective 6-year follow-up study. *Geriatrics & Gerontology International* 2008;8(3):172-9.
- [15] Yilmaz MI, Qureshi AR, Carrero JJ, et al. Predictors of carotid artery intima-media thickness in chronic kidney disease and kidney transplant patients without overt cardiovascular disease. *Am J Nephrol* 2010;31(3):214-21.
- [16] Ekart R, Hojs R, Pecovnik-Balon B, et al. Blood pressure measurements and carotid intima media thickness in hemodialysis patients. *Ther Apher Dial* 2009;13(4):288-93.
- [17] Szeto CC, Chow KM, Woo KS, et al. Carotid intima media thickness predicts cardiovascular diseases in Chinese predialysis patients with chronic kidney disease. *Journal of the American Society of Nephrology* 2007;18(6):1966-72.
- [18] Kawamoto R, Ohtsuka N, Kusunoki T, et al. An association between the estimated glomerular filtration rate and carotid atherosclerosis. *Intern Med* 2008;47(5):391-8.
- [19] Kawamoto R, Ohtsuka N, Ninomiya D, et al. Association of obesity and visceral fat distribution with intima-media thickness of carotid arteries in middle-aged and older persons. *Internal Medicine* 2008;47(3):143-9.
- [20] Kawamoto R, Tomita H, Oka Y, et al. Metabolic syndrome amplifies the LDL-cholesterol associated increases in carotid atherosclerosis. *Internal Medicine* 2005;44(12):1232-8.
- [21] Homocysteine Studies Collaboration. Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. *JAMA* 2002;288(16):2015-22.
- [22] Ridker PM, Rifai N, Rose L, et al. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 2002;347(20):1557-65.
- [23] Gerstein HC, Mann JF, Yi Q, et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA* 2001;286(4):421-6.
- [24] Drueke T, Witko-Sarsat V, Massy Z, et al. Iron therapy, advanced oxidation protein products, and carotid artery intima-media thickness in end-stage renal disease. *Circulation* 2002;106(17):2212-7.
- [25] Zoccali C, Benedetto FA, Maas R. Asymmetric dimethylarginine, C-reactive protein, and carotid intima-media thickness in end-stage renal disease. *J Am Soc Nephrol* 2002;13(2):490-6.
- [26] Honda H, Qureshi AR, Heimbürger O, et al. Serum albumin, creatinine, interleukin 6, and fetuin A as predictors of malnutrition, cardiovascular disease, and mortality in patients with ESRD. *Am J Kidney Dis* 2006;47(1):139-48.