

To Study the Correlation of Carotid Intimal - Medial Thickness with Estimated Glomerular Filtration Rate in Patients of Diabetes Mellitus Type 2

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Abstract: ***Aim:** To study the correlation of Carotid intimal - medial thickness with Estimated glomerular filtration Rate in patients of diabetes mellitus Type 2 **Material and methods:** In the present study, a total of 50 patients were enrolled out of which 25 were diabetic. For all the patients, eGFR was calculated using crockford gault formula and mean CIMT was measured and then compared to 25 non diabetic patients. Correlation was then observed between change of CIMT with every stage of CKD for both groups. **Results:** There was a consecutive increase in mean CIMT for both diabetic and non diabetic population with worsening of eGFR and progression in stage of CKD. **Conclusion:** Patients with diabetes have higher mean CIMT when compared to non diabetic patients and there was an observed increase in mean CIMT with worsening of the eGFR or progression of stage of CKD. Mean CIMT was higher in patients with uncontrolled diabetes as compared with those with controlled diabetes.*

Keywords: Carotid intimal - medial thickness, diabetes mellitus, glomerular filtration rate, chronic kidney disease

1. Introduction

Diabetes mellitus is a clinical syndrome characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both.¹ One of the major macrovascular complications of diabetes is increased risk of cardiovascular diseases (CVDs) which is one of the leading cause of death globally, taking an estimated 17.9 million lives each year.² High cardiovascular risk in patients with diabetic nephropathy is comparable with the increased cardiovascular risk of patients with coronary heart disease.³

Diabetes is a major risk factor in itself along with it causes early progression of chronic kidney disease and also predisposes the vessels to atherosclerosis.⁴ Coronary angiography remains the gold standard for assessing the degree of coronary atherosclerosis; however this invasive method is related with non - negligible morbidity especially in patients with hemodynamic instability. Thus there is an urgent need to develop non invasive screening methods for diagnosing atherosclerosis. Carotid intimal medial thickness

(CIMT) is a surrogate marker for the presence and progression of atherosclerosis and is a 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.⁵ Carotid intimal medial thickness is a simple, reproducible and non - invasive diagnostic method for evaluating the risk and preventing the incidence of cardiovascular events by early intervention. Intimal medial thickness is measured between the intimal luminal and the medial adventitial interfaces of the carotid artery.⁶

CIMT provides the benefit of quantifying atherosclerosis much earlier in its development in individual subjects with significant risk factors for cardiovascular disease like CKD.⁷

Studies correlating CIMT with renal clearance are scanty especially in the North Indian population. In this study we intend to see the correlation between CIMT and estimated GFR in patients of type 2 diabetes mellitus.

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2. Materials and Methods

In this study participants were patients attending the outpatient department as well as indoor patients of Guru Nanak Dev Hospital attached to Government Medical College, Amritsar. Group A included 25 type 2 diabetic males and females and Group B had 25 non diabetic males and females above the age of 20 years. The study was conducted after approval from the Institutional Ethics Committee, Government Medical College, Amritsar. Written and informed consent was taken from every patient. Detailed history including the duration of diabetes was taken and through general and systemic examination was done. Then hemoglobin, total leukocyte count, fasting blood glucose, blood urea, serum creatinine, complete lipid profile and ECG were recorded. The intimal medial thickness of carotid arteries was determined by using high resolution B mode ultrasonography system using electrical linear transducer of mid frequency of 7.5 MHz. The intimal medial thickness of carotid was defined as distance from leading edge of first echogenic line to second echogenic line. The first echogenic line represents the lumen intimal interface and the second line was produced by collagen containing the upper layer of the intimal adventitia. At longitudinal projection determination of intimal medial thickness was conducted at the side of greatest thickness and two points 1 cm upstream and 1 cm downstream from the side of greatest thickness. Total 6 intimal medial thickness measurements were taken 3 on the right side and 3 on the left side and their mean were representative values for each subject. All scans were conducted by trained ultrasonologist in the department of radio diagnostics, Govt. Medical College Amritsar who was not aware about the clinical status of study patients.

Inclusion Criteria:

- Patients diagnosed with diabetes using any of the given criteria.
- Symptoms of diabetes plus random blood glucose concentration ≥ 11.1 mmol/L (200 mg/dL) or
- Fasting plasma glucose ≥ 7.0 mmol/L (126 mg/dL) or
- Hemoglobin A1c $\geq 6.5\%$ or
- 2 - h plasma glucose ≥ 11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test.
- Patient with kidney damage or GFR < 60 ml/min/1.73m² for 3 months or more
- Kidney damage was defined as pathological abnormalities or markers of damage including abnormalities in blood or urine tests or imaging studies.

Exclusion Criteria:

- Patients with any evidence of arteritis or connective tissue disorders
- Patients having type 1 diabetes mellitus
- Patients already operated for carotid stenosis
- Endocrine disorder or any other significant illness
- Diabetics duration less than 5 years, no signs of DR, diagnosis of obstructive uropathy, active cancer or acute illness

Type of Study: Observational study

Statistical Analysis: At the end of study, the data was collected and was analysed using appropriate statistical methods. The statistical software SPSS was used for statistical analysis. The mean \pm standard deviation was calculated. Pair - wise comparison between the cases and controls were performed for all parameters using Student's unpaired t - test. The values of P < 0.05 was considered as significant. The qualitative variables were compared using the chi - square test. Univariate correlation analysis was used to confirm the significance of the variables of the CIMT.

3. Observations and Results

The predominant age group of the study population was 41 - 50 years. The mean age of diabetic population (Group A) was 44.52 ± 14.72 years and the mean age of the non diabetic population (Group B) was 45.68 ± 9.87 . This difference was statistically non significant (p value > 0.05)

There was almost equal sex distribution between both diabetic (Group A) and non diabetic population (Group B) with slight male predominance seen in diabetic and slight female predominance seen in non diabetic population.

Mean BMI was higher in diabetics (Group A) as compared to non diabetics (Group B). However the difference between the two groups was not statistically significant with (p value > 0.05).

There was a consecutive increase observed in mean CIMT with increase in age of the diabetic patients. Mean CIMT was more in diabetic patients (Group A) of every age group when compared to non diabetic patients (Group B)

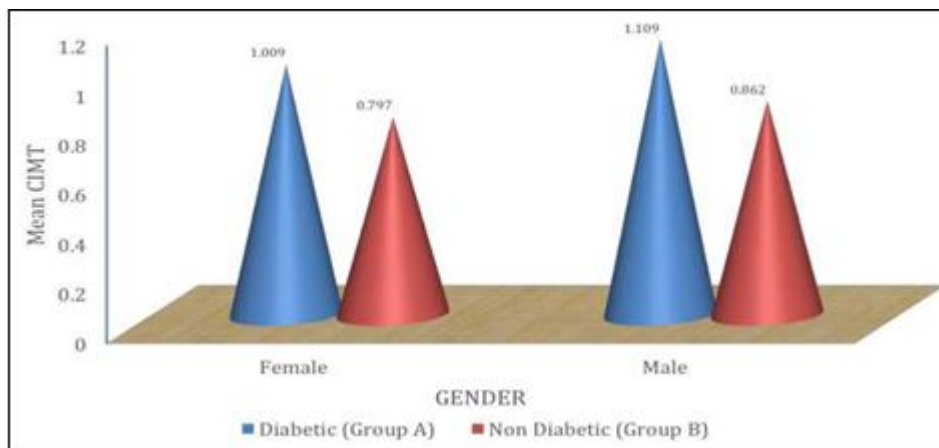
Table 6: Correlation of Mean CIMT with Age

Age Group	Mean CIMT				p- value
	Diabetic (Group A)		Non Diabetic (Group B)		
	Mean	SD	Mean	SD	
<30	0.600	0.00	0.716	0.275	0.749
31- 40	1.000	0.101	0.896	0.128	0.187
41- 50	1.013	0.181	0.755	0.251	0.019
51- 60	1.025	0.176	0.950		0.788
61- 70	1.063	0.251	0.900	0.324	0.394
> 70	0.67	0.000	-	-	-
Total	1.007 \pm 0.196		0.828 \pm 0.219		0.004

Mean CIMT of diabetic patients (Group A) is 1.007 ± 0.196 while mean CIMT of non diabetic patients (Group B) was 0.828 ± 0.219 . This observed difference between the two groups was statistically significant (p value < 0.05). Mean CIMT was higher in both diabetic (Group A) males and females as compared to non diabetic (Group B) males and females

Table 7: Correlation of Mean CIMT with Gender

Sex	Mean CIMT				p- value
	Diabetic (Group A)		Non Diabetic (Group B)		
	Mean	SD	Mean	SD	
Female	1.009	0.239	0.797	0.263	0.062
Male	1.109	0.165	0.862	0.163	0.029
Total	1.007 \pm 0.196		0.828 \pm 0.219		0.004



Mean CIMT was higher in diabetic smokers (Group A) as compared to diabetic non smokers (Group A). However this difference was statistically non - significant (p value>0.05).

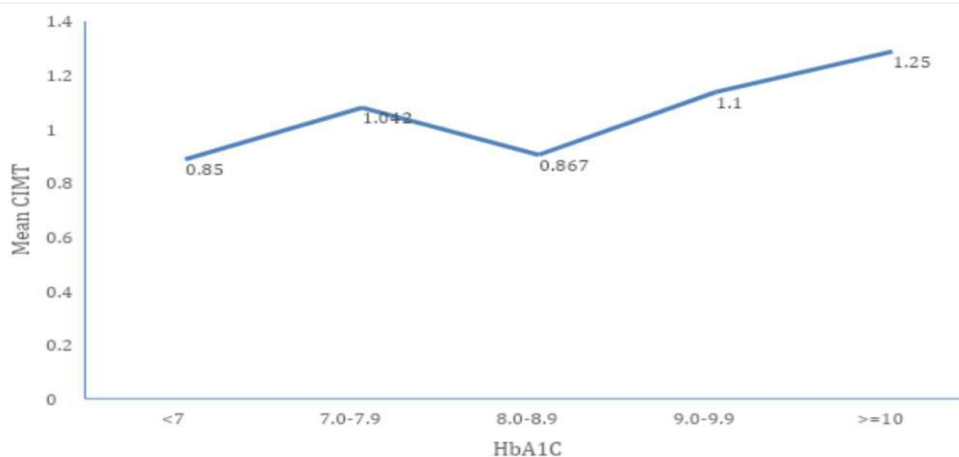
Mean CIMT was higher in diabetic alcoholics (Group A) as compared to diabetic non alcoholic patients. However this difference was statistically non - significant (p value>0.05).

Total mean LDL, total serum cholesterol and total triglyceride levels were higher for diabetic population (Group A) as compared to non diabetic population (Group

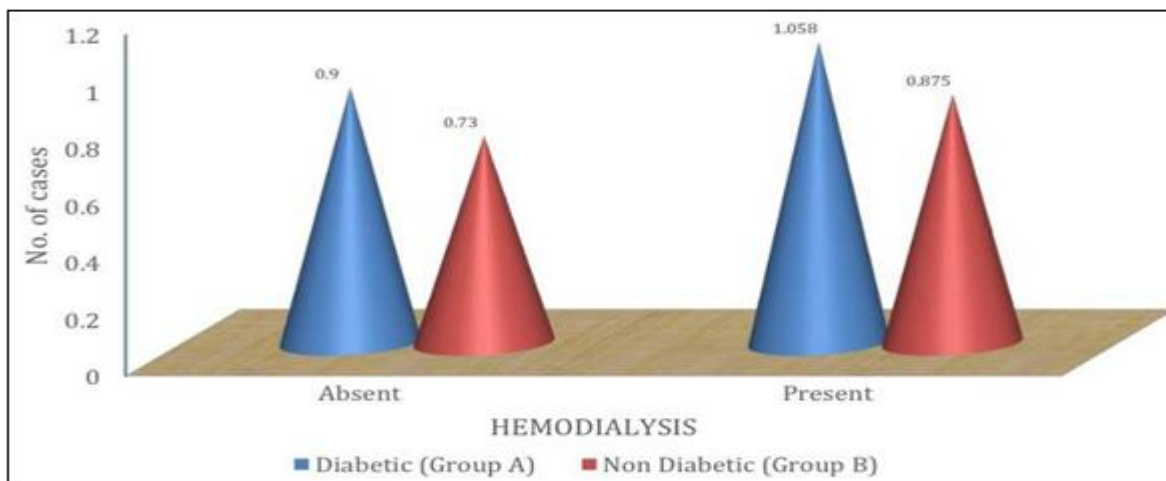
B). However this difference was statistically non - significant (p value >0.05).

Higher mean CIMT was seen in diabetic (Group A) as well as non diabetic (Group B) with higher serum LDL, serum cholesterol and serum triglyceride levels.

There was an overall consecutive increase observed in mean CIMT levels with increase in HbA1c levels. Maximum mean CIMT (1.25 mm) in diabetic population was seen in patients with HbA1c levels > 10.



Diabetic patients on hemodialysis had mean CIMT more than patients on hemodialysis without diabetes and this difference was statistically significant (p value <0.05).



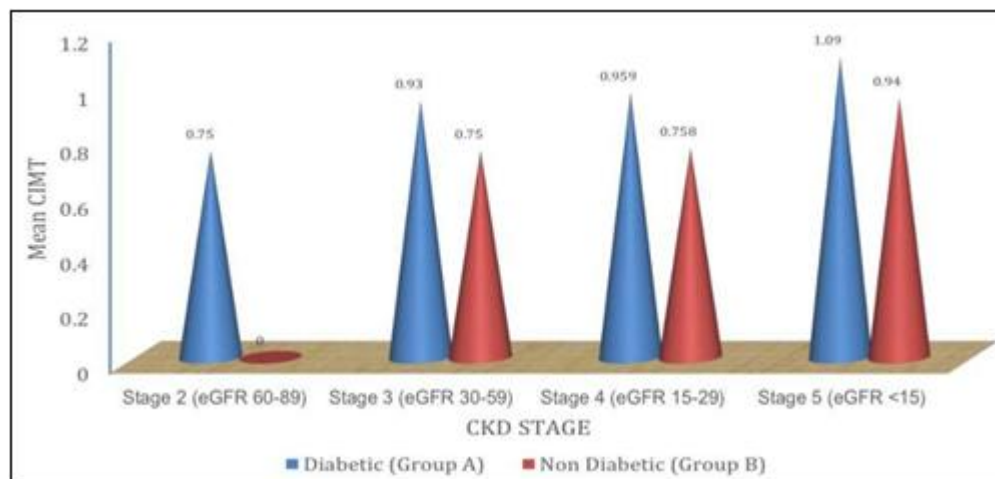
Majority of the study population both diabetic (Group A) and non diabetic (Group B) belonged to the stage 5 CKD with eGFR <15

Table 2: Distribution of Patients according to the Stage of CKD and eGFR

CKD stage	Diabetic (Group A)		Non Diabetic (Group B)	
	No.	%age	No.	%age
Stage 2 (eGFR 60 - 89)	1	4	0	0
Stage 3 (eGFR 30 - 59)	5	20	6	24
Stage 4 (eGFR 15 - 29)	7	28	9	36
Stage 5 (eGFR <15)	12	48	10	40
Total	25	100	25	100

χ^2 : 1.523; df: 3; p=0.677

With worsening of the stage of CKD i. e. with fall of eGFR there was a consecutive increase observed in mean CIMT levels in both diabetic (Group A) as well as non diabetic population (Group B). For every stage of CKD mean CIMT levels were more in diabetic population (Group A) as compared to non diabetic population (Group B) and this difference between the two groups was statistically significant (p value <0.05) for every stage of CKD



Graph 3: Correlation of Mean CIMT with Stage of CKD and EGFR

4. Discussion

The study population was divided into two groups namely group A that included 25 diabetic patients of both sexes of different ages and group B that included 25 patients without diabetes of both the sexes. The predominant age group of the diabetic population as well as non diabetic population was 41 - 50 years with mean age of the diabetic population being 44.52±14.72 years while that of the non diabetic population was 45.68 ±9.87 years. This mean age of patients with CKD indicates that a large proportion are in their economically productive years, that is, less than 60 years of age, unlike what is observed in industrialized countries where the peak age of presentation is 65 to 74 years. Similar to our study Chhajed et al also had a study population with mean age of 44.5 years.⁸ While Roumeliotis et al reported the mean age of the diabetic population as 68 years.⁹

When gender distribution was compared among both the groups it was seen that both groups had an almost equal distribution of males and females with the slight predominance of males in group A whereas group B had slight female preponderance. Niskanen et al also had a similar study population with a slight male predominant diabetic population¹⁰ Their study had 43 (51.1%) males and 41% females (48.8%) Roumeliotis et al. also enrolled similar numbers of diabetics comprising 54% of males and 46% of females.⁹

In our present study hypertension was the most common risk factor in non diabetic patients (group B) and the diabetic patients (group A). In concordance to our study Buren et al. also reported hypertension is highly prevalent in patients with type 2 diabetes and nephropathy.¹ In a study done by Niskanen et al 56% of patients with diabetes were hypertensive whereas only 45.9 % of patients with normal glucose tolerance had hypertension. Their study also reported similar prevalence of smoking and obesity between the two groups.¹⁰

It was seen that there was no statistically significant difference in mean systolic blood pressure, diastolic blood pressure as well as pulse rate between two groups. Similar results were also reported by Niskanen et al with mean SBP 153 mmHg and mean DBP 84 in diabetic population and mean SBP 147 and mean DBP 86 mm Hg in non diabetic population. Similar to our study, no statistically significant difference was observed.¹⁰

Mean CIMT for both males as well females was higher for diabetic population as compared to non diabetic population. This difference between the two groups was statistically non-significant (p value >0.05) for females however a slightly statistically significant difference was seen for males. In concordance to our study Niskanen et al also reported a higher mean CIMT for diabetic males (1.65 ± 0.77 mm) and for females (1.68 ± 0.07 mm) when compared to non diabetic males (1.49±0.06 mm) and for females (1.41 ±0.07 mm). Similar to our study this difference was not

statistically significant for both females while a slightly statistically significant difference was seen for males (p value <0.05).¹⁰

In our present study diabetic smokers had a higher mean CIMT as compared to mean CIMT in diabetic non smokers but this difference was not statistically significant. Similar increase in mean CIMT was observed for non diabetic smokers as compared to non diabetic non smokers and this difference was also not statistically significant. In concordance to our study Pan et al also reported a significantly higher CIMT in diabetic patients with history of smoking as compared to non diabetic with no history of smoking.¹² Roumeliotis et al also reported that in patients with higher mean CIMT (>0.86mm) had more duration of smoking as compared to the patient with normal mean CIMT and similar to our study this difference was not statistically significant.⁹ Kato et al also reported similar weak but significant and positive relationship between log IMT and habitual smoking subjects.¹³

In our study diabetic (Group A) alcoholic patients had a higher mean CIMT as compared to mean CIMT in diabetic (Group A) non alcoholic but this difference was not statistically significant. Similar increase in mean CIMT was observed for non diabetic (Group B) alcoholics as compared to non diabetic (Group B) non alcoholics and this difference was also not statistically significant. In concordance to our study Pan et al also reported significantly increased CIMT in patients with alcohol use in comparison to patients with no history of alcohol consumption.¹²

It was also seen that mean CIMT was higher in diabetic patients (Group A) as well as non diabetic patients (Group B) with higher levels of mean LDL, triglycerides and cholesterol levels. Diabetics with deranged lipid profile had a higher mean CIMT as compared to non diabetics. Out of the lipid profile only increase in total cholesterol increased the mean CIMT significantly for non diabetics however could not increase it significantly in diabetics, still diabetics with higher total cholesterol had higher mean CIMT than non diabetics with higher total cholesterol signifying that diabetes is a predominant risk factor for increasing CIMT. In concordance to our study Chhajed et al also reported a higher mean CIMT in patients with higher total cholesterol and triglyceride levels as compared to those with normal levels and this difference was statistically significant.⁸ In concordance to our study Pan et al also concluded that the levels of TC, TG, HDL - C, and LDL - C are associated significantly with higher mean CIMT.¹² Roumeliotis et al also concluded that in patients with higher mean CIMT (>0.86mm) in patients with higher total cholesterol, serum triglycerides however similar rise was not seen in serum LDL levels.⁹ Niskanen et al reported no difference in serum total LDL and cholesterol levels between the two groups however, total triglyceride levels increased with worsening of glucose tolerance status.¹⁰

In our study the majority of the diabetic population (Group A) had HbA1c levels between 7.0 - 7.9%. Only 16% of the patients with diabetes had controlled diabetes with HbA1c of <7%. Mean HbA1c of diabetic population was 7.77±0.95%. It was also observed that mean CIMT increased with

increase in the levels of HbA1c demonstrating the significant influence of quality of blood sugar control on mean CIMT.

In concordance to our study, Kotb Et al. also reported a significantly higher mean CIMT in patients with uncontrolled diabetes as compared to patients with controlled diabetes. Mean HbA1c in their study was 7.5 ± 1.7%.¹⁴

Higher mean CIMT was seen in diabetic patients (Group A) on hemodialysis as compared to the non diabetic patients (Group B) on hemodialysis. Similar increase in mean CIMT was observed in diabetic patients (Group A) with no history of hemodialysis compared to non diabetic patients (Group B) without dialysis however this difference was not statistically significant. In concordance to our study Hojs et al also reported higher IMT values of the common carotid and internal carotid arteries in hemodialysis patients than in controls.¹⁵

Kato et al also reported that mean carotid artery IMT was significantly higher in those patients who expired on hemodialysis compared with that in the survival group. They also concluded that dialyzer membrane did not influence mean IMT and there was no association between carotid intimal thickness and the product of calcium and phosphate.¹³

Our study had the majority of the diabetic (Group A) as well as non diabetic (Group B) population in stage 5 CKD as earlier stages of CKD are usually asymptomatic; majority of the patients in developing nations seek medical assistance only during the advanced stages. As the stage of CKD and eGFR worsens there was an increase observed in the mean CIMT for both diabetic (Group A) as well as non diabetic patients (Group B). Mean CIMT of diabetic population (Group A) and non diabetic population (Group B) with eGFR >30 was 0.9 ±0.2 mm and 0.75 ±0.17 mm respectively). Diabetic patients had a higher mean CIMT for every stage of CKD when compared to every corresponding stage in non diabetic patients. The increase observed was more in diabetic population as compared to the non diabetic population and this increase in our study was statistically significant for every stage of CKD. In concordance to our study Roumeliotis et al also observed significant increase in the CIMT and with worsening of the eGFR.⁹ Kuswardhani et al also reported that subjects on maintenance hemodialysis (mHD) with CVD had higher CIMT values than those without CVD.¹⁶ Similarly, Zhang et al in their study on stage 2 - 3 CKD patients found significantly increased CIMT and concluded that arterial change might occur in the early stages of CKD.¹⁷ Margekar et al. inferred that increased cardiovascular risk can be determined by measuring the carotid arterial wall thickness and CKD patients have significantly more carotid arterial wall thickness. However contrary to our no significant difference in the CIMT was observed in different stages of CKD.¹⁸

5. Conclusion

Diabetes is a risk factor for the development of atherosclerosis, primarily affecting elastic arteries (carotid arteries and aorta). Cardiovascular risk are increased more in patients of renal disease as compared to the general population. From our present study we concluded that CIMT measurement is a relatively cheap, safe, noninvasive, reproducible, and precise method of examining and evaluating the walls of carotid arteries. The thickening of the intima-media complex reflects generalized atherosclerosis which is the basis for both microvascular and macrovascular complication of diabetes. CIMT was also found to be higher in diabetic patients as compared to non diabetics and consecutive increase was observed with worsening of eGFR

CIMT can thus be used as a non - invasive marker for systemic atherosclerosis and can be considered by further studies as a screening marker of both macrovascular and microvascular complication of diabetes like nephropathy.

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