Original Research Article

Carotid artery intima media thickness in relation with atherosclerotic risk factors in patients with newly diagnosed type 2 diabetes mellitus in a rural tertiary care hospital in central India

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ABSTRACT

Background: Vascular complications of atherosclerosis are major causes of morbidity and mortality in patients with type 2 diabetes mellitus (T2DM). The aim of the study was to study the correlation between carotid artery intima media thickness (CIMT) and risk factors for atherosclerosis and atherosclerotic vascular events in newly diagnosed type 2 diabetes mellitus patients with an objective to determine the predictive value of CIMT as an indicator of early atherosclerosis.

Methods: The predictive value of CIMT as well as various atherosclerotic risk factors including ankle brachial index (ABI) were determined as an indicator of early atherosclerosis. Data were presented in form of percentage and proportions. Qualitative variables were tested using Chi square test and the p values were calculated between the groups having CIMT less than and more than 0.9 mm. p values of ≤0.05 were considered statistically significant. Averages were expressed between groups as mean ±standard deviation or as percentage. Multivariate analysis was done using the multiple linear regression model.

Results: The study showed that though age, smoking and dyslipidemia did not show any association with CIMT; hypertension, ABI, glycosylated hemoglobin and urine albumin excretion rate had positive correlation with CIMT with statistically significant association between ABI and CIMT.

Conclusions: Assessment of CIMT by B mode ultrasound is a relatively inexpensive means of measuring subclinical atherosclerosis. Present study showed that CIMT is significantly higher in those type 2 diabetic patients who had atherosclerotic events than in those type 2 diabetic patients who had only risk factors for atherosclerosis.

Keywords: Atherosclerosis, Ankle brachial index, Carotid intima media thickness, Diabetes mellitus

INTRODUCTION

Vascular complications of atherosclerosis are major causes of morbidity and mortality in type 2 diabetes patients in India, where number of diabetic patients is on rise. Accelerated atherosclerosis occurs in diabetic patients at the same time in carotid, cerebral, peripheral and coronary arteries as suggested by the atherosclerotic risk project.[1] Intima Media Thickness of Carotid Artery (CIMT) can be measured with high degree of accuracy by the B mode ultrasonography which provides reliable and valid estimate of the arterial wall thickness. B mode ultrasound is recommended by American heart association as relatively safe, noninvasive and inexpensive method of assessing subclinical atherosclerosis.[2] CIMT being an independent predictor of atherosclerotic events, present study was carried out to know the relationship of carotid artery intima media thickness with risk factors for atherosclerosis and with atherosclerotic vascular events in patients with type 2

diabetes mellitus.[3] CIMT is measured at near wall and far wall of the proximal 10mm of the internal carotid artery, the carotid bifurcation beginning at the tip of the flow divider and extending 10mm below this point.[4] The question is what is the relation of carotid intima media thickness and risk factors for atherosclerosis in patients with newly diagnosed type 2 diabetes mellitus in a rural tertiary care hospital in central india. The aim of the study was to study the correlation between CIMT and risk factors for atherosclerosis and atherosclerotic events in newly diagnosed type 2 diabetes mellitus patients. The objectives of the study were to determine the predictive value of CIMT as an indicator of early atherosclerosis and to study the various atherosclerotic risk factors in type 2 diabetes mellitus patients.

METHODS

This cross-sectional study was carried out in the department of internal medicine UPUMS Saifai, Etawah for a period of 18months starting from Jan 2015 to June 2016. Newly diagnosed patients with type 2 diabetes mellitus treated in IPD and OPD of the department of internal medicine UPUMS Saifai, Etawah were randomly included in the study. The criterion used for the diagnosis of diabetes was fasting plasma glucose ≥126mg/dl or 2hour post prandial/OGTT plasma glucose ≥200mg/dl or symptoms of hyperglycemia and random plasma glucose ≥200mg/dl.[5] Newly diagnosed were the patients which were diagnosed with T2DM either at presentation or within 6months of presentation. Those patients with type 1DM, secondary DM, overt renal failure, congestive heart failure, urinary tract infection, acute coronary syndrome or recent intercurrent illness were excluded from the study. All patients studied underwent:

Detailed assessment of history with stress on risk factors for atherosclerosis and atherosclerotic events. Thorough general physical examination including anthropometric measurements and systemic examination for atherosclerotic vascular disease. For BMI (body mass index) a cut off value of 23kg/m² was adopted for this study as per the WHO standards for Asian Indians. For measuring waist circumference, a point at the highest point of iliac crest crossing the mid axillary line on the right side of trunk was taken and the circumference was measured horizontally at normal respiration. Hip circumference was measured at the widest point between the hips and buttocks. Waist hip ratio (WHR) was defined as the waist circumference divided by the hip circumference. Cut off values for waist circumference were 90cms and 80cms for men and women respectively, and the corresponding waist-hip ratios were 0.88 and 0.81 for men and women respectively as per the WHO standards for Asian Indians.[6]

Routine and special investigations including fasting and 2hour post prandial plasma glucose, lipid profile, ECG, urine microalbumin-creatinine ratio and glycosylated hemoglobin were performed in all patients.

The fasting plasma glucose (FPG) and fasting lipid profile (FLP) were obtained after at least 12hours of overnight fasting using the Randox auto analyzer and the 2hour post prandial plasma glucose (PPBG) estimation was also done. The value of LDL was calculated using the Freidwald's formula when the values of triglycerides were less than 400mg/dl and direct estimation was done when triglyceride values were more than 400mg/dl. Dyslipidemia was defined based on the National Cholesterol Education Programme ATP3 (NCEP ATP3) guidelines and the normal cut off values were taken as total cholesterol less than 200mg/dl; LDL less than 100mg/dl; triglyceride less than 150mg/dl and values outside these limits were considered as abnormal. For HDL cholesterol a value less than 40mg/dl was considered low as per NCEP-ATP3 guidelines.[7]

Glycosylated hemoglobin (HbA1C) was estimated by column chromatography method. Patients were categorized as those having a HbA1C value of less than 7.5% which indicates good control of diabetes and those having HbA1C values more than 7.5% which indicate poor glycemic control. The Ankle Brachial Index(ABI), a surrogate marker of atherosclerosis, was calculated as the ratio of ankle systolic blood pressure as the numerator over the higher brachial systolic blood pressure as the denominator.[8]

Carotid artery intima media thickness (CIMT) was measured by the B mode ultrasound having a transducer with a mid-frequency of 7.5 MHz. Scans were performed on both the right and left extracranial carotid arteries. The CIMT values were measured in six well defined arterial segments-near walls and far wall of distal 6mm of common carotid, the carotid bulb and proximal 6mm of internal carotid arteries on both the sides. The final CIMT considered was the average of the CIMT values at the 12 sites examined. Since CIMT is considered as a candidate marker of cardiovascular risk, its normal value is interpreted in terms of increased risk rather than in terms of statistical distribution within a population. An upper limit of 0.9mm was chosen for the present study based on epidemiological data currently available.

Statistical analysis

Data were presented in form of percentage and proportions. Qualitative variables were tested using Chi square test and the p values were calculated between the groups having CIMT less than and more than 0.9mm. p values of ≤0.05 were considered statistically significant. Averages were expressed between groups as mean ±standard deviation or as percentage. Multivariate analysis was done using the multiple linear regression model.

RESULTS

A total of 60 patients were studied of which 70% were males and all of them fulfilled inclusion and exclusion

criteria. The bias in the sex proportion was in concordance with the statistics of indoor admissions and OPD visits. 30% of the study population had prior hypertension which was adequately controlled during the course of study. The mean age of patient cohort was 46.8 years. All patients enrolled in the study were newly diagnosed diabetics either diagnosed at presentation or within 6 months of their presentation. Though the waist circumference was normal in 48% of patients, 79.3% of patients had abnormally high waist-hip ratio. The mean values of various parameters expressed between the groups with a CIMT less than and more than 0.9mm were calculated. Clinical and biochemical characteristics are presented in Table 1.

Table 1: Means of variables compared between the groups.

Variable	Mean±1SD		P value
	CIMT<0.9	CIMT>0.9	
WC (cms)	83.6 (9.1)	86.2 (11.6)	0.60
W/H ratio	0.93 (0.09)	0.98 (0.07)	0.02
BMI (kg/m²)	22.1 (2.9)	23.4 (3.8)	0.42
FBS	163.45(67.8)	184.2(48.9)	0.47
PPBS	208.4 (78.2)	206.2 (58.3)	0.87
T. Chol.	187.8 (37.9)	201.2 (39.7)	0.23
TGL	132.8 (29.2)	147.3 (45.2)	0.12
HDL	41.4 (7.8)	40.8 (9.1)	0.73
VLDL	22.9 (5.7)	27.3 (9.8)	0.11
LDL	116.6 (29.2)	123.6 (32.2)	0.34
CHO/HDL	5.38 (3.9)	5.56 (1.3)	0.39
UACR	293.1 (723.3)	234.7(876.9)	0.64
HBA1C%	8.9 (2.8)	9.1 (2.1)	0.86

On comparing age with CIMT, no statistically significant association was found (p value 0.52). 46.2% patients had history or clinical manifestations suggestive of atherosclerotic macrovascular disease at presentation or during the course of study. 68.2% of patients had albuminuria with majority having microalbuminuria. Patients with and without increased carotid artery intima media thickness were equally distributed in our study population and only 6 patients had demonstrable plaque by ultrasound. 64.3% patients with microalbuminuria depicted increased CIMT values greater than 0.9mm with p value only nearly significant (p value: 0.07) (Figure 1).
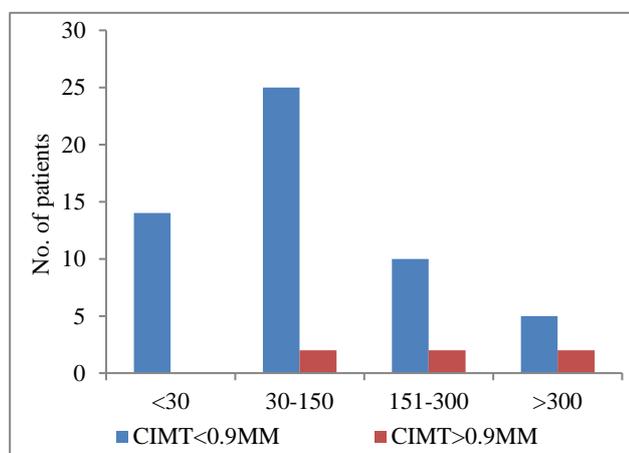

Figure 1: Association of Albuminuria with CIMT.

68.68% of those with hypertension had increased intima media thickness with a nearly significant p value of 0.06 (Figure 2).
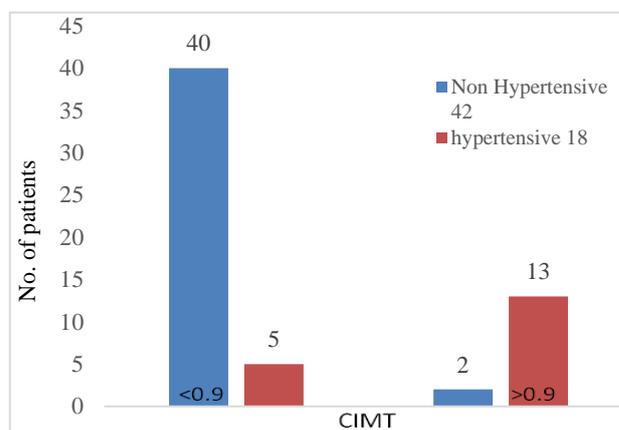

Figure 2: Association of Hypertension with CIMT.

Though waist circumference and body mass index (BMI) had no correlation with CIMT, it was found that 95% of those with increased CIMT had abnormal waist-hip ratio with a significant p value of 0.004 (Figure 3). 50% of the patients had previous atheroembolic events of which 66.67% had increased CIMT and the p value for this observation was statistically significant with p value of 0.014 (Figure 4). 76.46% of those with HbA1C values greater than 8% indicating poor control of diabetes had

increased average intima media thickness with a significant p value of 0.004 (Figure 5). All patients with HbA1C values greater than 8% had increased urine albumin excretion rate either in the microalbuminuric range (78.6%) or in the macroalbuminuric range (21.4%).
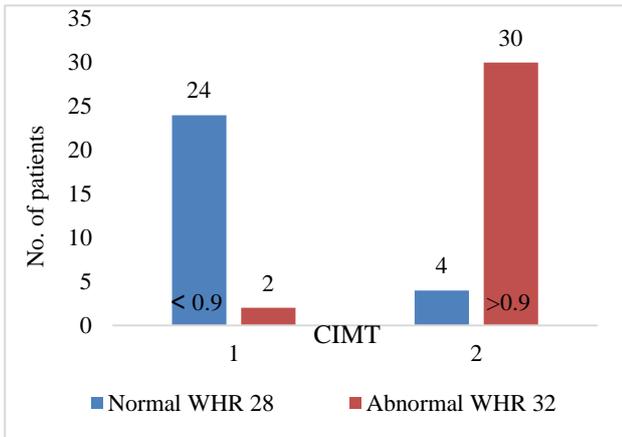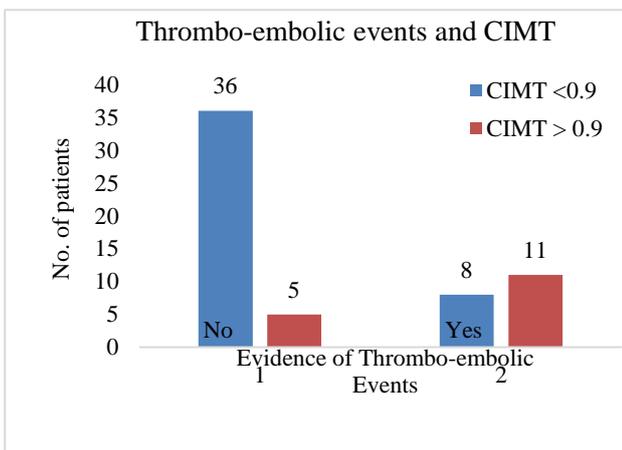

Figure 3: Association of WHR with CIMT.

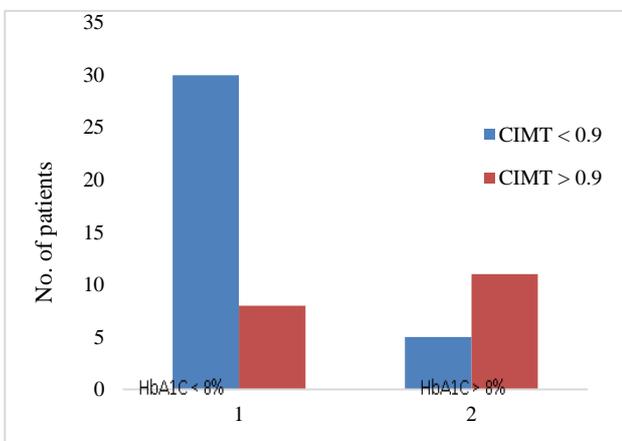**Figure 4: Association of presence of Thrombo-embolic events with CIMT.**

Figure 5: Association of HbA1C with CIMT.

20.2% of the patient population had ankle-brachial pressure index (ABI) values lesser than 0.9 of which 94.7% had CIMT values greater than 0.9mm and the p value for this association was highly statistically significant with p value of 0.0001 (Figure 6). Smoking and dyslipidemia was not found to have any association with carotid intima media thickness.
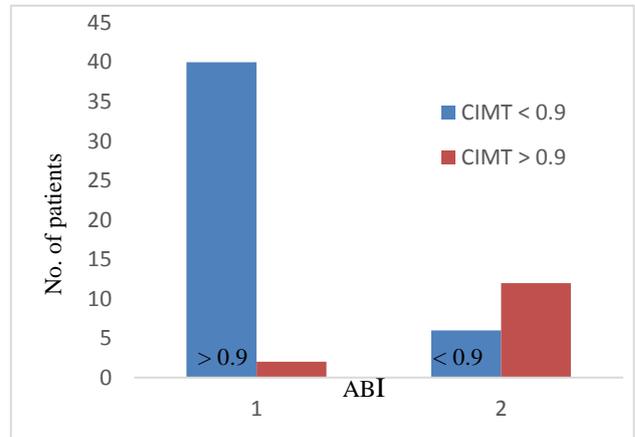

Figure 6: Association of CIMT with ABI.

The factors which were statistically significant in univariate analysis were considered for multivariate analysis by multiple linear regression model. Among the various variables the maximum significance was obtained with ABI and evidence of atheroembolic disease with a p value of 0.03 and 0.04 respectively (Table 2).

Table 2: Multivariate analysis.

Variable	Coefficient	Std. Error	F-test	P-value
Atheroembolic disease	0.259	0.143	3.4307	0.07034
Duration of diabetes	0.064	0.173	0.1398	0.70088
Hba1c	0.062	0.058	0.6789	0.40187
Hypertension	0.194	0.179	0.9087	0.34084
UACR	0.045	0.098	0.5678	0.47898
W/h ratio	0.301	0.109	3.6543	0.05321
Constant	0.123	0.432	0.1243	0.67543

DISCUSSION

Measurement of carotid artery intima media thickness by noninvasive B mode ultrasonography can detect subclinical atherosclerosis and therefore, helps in early diagnosis and treatment of asymptomatic atheroembolic macrovascular disease among diabetics and whether increased CIMT is associated with increased risk of atherosclerotic events is of considerable interest. In the present study, a total number of 44 patients were studied and the majority of patients were in the 4th to 6th decade. The overall prevalence of albuminuria was 81.81% of which 54.5% were in the microalbuminuric range. There was no statistically significant correlation between

albuminuria and the duration of diabetes in our study which is comparable to studies from other parts of India.[9] It was also observed that urine albumin excretion rate was associated well with the level of glycemic control and it was found that those with good glycemic control had lower albumin excretion rates, but no association could be obtained between hypertension and prevalence of albuminuria. Midha and Khurana et al followed up 76 patients with type 2 DM and found that the change in the pattern of microalbuminuria did not correlate with the age, sex and duration of diabetes and those who showed decrease in microalbuminuria had good glycemic control.[10] On the other hand Saini et al noticed that microalbuminuria was more common in patients with longer duration of diabetes, a poor glycemic control.[11] The overall prevalence of retinopathy in our study was 72.72%.

There was a strong correlation between albuminuria and retinopathy with a significant P value of 0.0005. The results are comparable with that of Masoud Manaviat et al who also reported increased prevalence of retinopathy in patients with microalbuminuria and macroalbuminuria.[12] Masoud et al and Farhan et al had also noticed significant association between body mass index and retinopathy.[13] The same could not be obtained in our present study. The mean value of carotid artery intima media thickness in this study was 0.938mm. Similar mean value of 0.95 mm was reported earlier in a Chennai based study.[14] Females had a relatively lower value of CIMT as compared to males possibly due to the protective effect of female hormones and/or male gender being at a higher risk of atherosclerosis. Similar results have been reported by Kraml et al who also observed significant higher IMT in men than women.[15]

In our present study no correlation was observed between age and intima media thickness. Doruk et al noticed that there was no significant correlation between age and carotid artery IMT.[16] On the other hand Robin et al reported that IMT was independently and positively related to age.[17] It was also observed that the IMT increased with the duration of diabetes with a significant p value of 0.0218.

The results obtained were similar to that of a Chennai based study who observed increased IMT with increasing duration of diabetes. It was also noticed that as albuminuria increased, the proportion of patients with raised intima media thickness also increased. 83.33% in the macroalbuminuric group had increased carotid artery intima media thickness.[18] Leena Mykannen et al, in the Insulin Resistance Atherosclerosis Study reported that subjects with microalbuminuria had greater Common carotid artery IMT than those without microalbuminuria. Similar results were demonstrated by Gilles FH Diercks et al, whose study showed that urine albumin excretion is strongly related to subclinical atherosclerosis (assessed by IMT) in type 2 diabetic patients.[19] The IMT was found to be higher among those with central obesity as assessed

by the waist-hip ratio with a highly significant P value of 0.004. But there was no definite association between body mass index and carotid artery intima media thickness. This again emphasizes the emerging concept that the body composition rather than the size may be more relevant risk factor for cardiovascular events. Waist hip ratio was found to be an independent determinant of IMT even on multivariate analysis. Mario et al in her study of association of obesity and central fat distribution with carotid artery wall thickening indicated a graded and independent association between general and abdominal obesity reflected by high BMI and WHR respectively and carotid wall thickening. Waist hip ratio was found to be an independent determinant of intima media thickness even after multivariate analysis.[20] 77.77% of the hypertensives in the present study had increased carotid artery intima media thickness.

The results are comparable to those of Matsumoto et al who observed that IMT correlated strongly with systolic blood pressure.[21] The level of glycemic control was yet another factor associated with carotid IMT. Though the p value was very much significant on univariate analysis it was found to be insignificant on multivariate analysis. Matsumoto et al observed that CCA IMT correlated strongly with HbA1c values.[22] In the present study dyslipidemia was not found to have statistically significant correlation with IMT. The risk factors for increased carotid artery intima media thickness in diabetic patients seem to be different in various studies. Geroulakos et al found that none of the potential risk factors (age, sex, body mass index, smoking, duration of diabetes, systolic or diastolic blood pressure, lipid profile, glycosylated hemoglobin) were associated with increased IMT in type 2 diabetics in their study.[23]

On the other hand, Temelkova-Kurktschiev et al noticed increased intima media thickness in diabetic patients with hyperlipidemia. Mohan Rema et al observed a positive correlation between duration of diabetes and increased intima media thickness. In our study, duration of diabetes, waist hip ratio, HbA1c and hypertension had statistically significant positive association with CIMT on univariate analysis of which only waist hip ratio was found to be significant after multivariate linear regression analysis.[24] The present study revealed that the CIMT in diabetic patients with atherosclerotic events was significantly higher as compared to carotid artery IMT in diabetic patients who had only risk factors for atherosclerosis, but no events with a P value of 0.0148.

Similar events were reported in the 'Atherosclerosis Risk in Communities' (ARIC) study who noticed increased intima media thickness in patients who had atherosclerotic events.[25] An observation was made in this study that of the 24 patients who had atherosclerotic events, majority (66.67%) had intima media thickness greater than 0.9mm. At the same time, of the 20 patients who had only risk factors for atherosclerosis but no events, majority (70%) had IMT less than or equal to

0.9mm. The association was significant even on multivariate regression analysis. In this way, the positive associations of increased CIMT with atherosclerotic vascular events may be of great implication and can help to screen high risk diabetic patients for atherosclerotic events. Close monitoring with feasible B mode ultrasonography can help in early and subclinical evaluation of the atherosclerotic process and event prediction in the diabetic patients who are always more prone to events.

CONCLUSION

Today complications due to atherosclerosis in diabetes are not only the most prevalent, but are the most challenging issue in this era of diabetic management. There has been a steady rise in the prevalence of atherosclerotic events among diabetics and the problem is more marked in those with Type 2 Diabetes Mellitus. Assessment of carotid artery intima media thickness by B mode ultrasound is a relatively inexpensive means of measuring subclinical atherosclerosis. Present study showed that carotid artery intima media thickness is significantly higher in those type 2 diabetic patients who had atherosclerotic events than in those type 2 diabetic patients who had only risk factors for atherosclerosis but no events. Microalbuminuria is strongly associated with the presence of retinopathy in type 2 diabetic patients and thus diabetic patients who have microalbuminuria may benefit from close ophthalmological follow up. Waist hip ratio showed a significant positive correlation and independent association with CIMT stressing the importance of lifestyle interventions in the management of diabetes mellitus. Duration of diabetes, urinary albumin excretion rate, hypertension and glycated hemoglobin had positive correlation with CIMT but could not assume statistical significance. Age, smoking and dyslipidemia did not show any association with carotid artery intima media thickness.

Thus, the predictive value of this non invasive investigation, may alert the clinician to the risk of events early enough to intervene, in order to prevent major cardiovascular or cerebrovascular catastrophes. Moreover, lifestyle measures and good glycemic control can pave the way for drastically reducing such catastrophes.

This may make a huge difference in the lives of diabetics, saving them from being between death, dependence or severe restriction in the quality of life, enforced by such events. Thus, it may ultimately help them to lead healthy and useful lives, which is the goal of all medical interventions.

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