Carotid Artery Intima Media Thickness in Relation with Atherosclerotic Risk Factors in Patients with Type 2 Diabetes Mellitus

R Gayathri*, R Chandni**, V Udayabhaskaran***

Abstract
The present study was carried out to study the correlation between carotid artery intima media thickness (CIMT) with risk factors for atherosclerosis and atherosclerotic events in Type 2 Diabetes mellitus patients. The predictive value of CIMT as an indicator of early atherosclerosis was determined and the various atherosclerotic risk factors in type 2 diabetes mellitus were studied. Our study showed that CIMT was significantly higher in those type 2 diabetic patients who had atherosclerotic events than in those patients who had no atherosclerotic events. It was also found that waist hip ratio showed a significant positive correlation and independent association with CIMT emphasizing the emerging concept of central obesity. 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 CIMT.

Introduction
Vascular complications due to atherosclerosis are a major cause of morbidity and mortality in type 2 diabetic patients, more so in India where the number of diabetics is approaching very high levels.1 Atherosclerosis which is the major risk factor is accelerated in diabetes mellitus. It has been suggested by the atherosclerotic risk project that the atherosclerotic process occurs at the same time in carotid, cerebral and coronary arteries.2 The intima media thickness (IMT) of the carotid artery (CIMT) can be measured with a high degree of accuracy and reproducibility by B mode ultrasonography which provides a reliable and valid estimate of the arterial wall thickness.3 Of the various non invasive imaging methods available, arterial intima media thickness measurement obtained by B mode ultrasound is currently recommended by the American Heart Association as being relatively safe, non invasive and inexpensive method of assessing sub clinical atherosclerosis,4 and being an independent predictor of atherosclerotic events. Therefore the present study was undertaken to know the relationship of carotid artery intima media thickness with risk factors for atherosclerosis and with atherosclerotic events in type 2 diabetes mellitus patients.

Aims and Objectives
• The aim of the study was to study the correlation between Carotid artery intima media thickness with risk factors for atherosclerosis and atherosclerotic events in type 2 diabetes mellitus patients.
• The objectives were
  1. To determine the predictive value of carotid artery intima media thickness as an indicator of early atherosclerosis
  2. To study the various atherosclerotic risk factors in type 2 diabetes mellitus.

Materials and Methods
The study was carried out in the department of General medicine, Medical College, Calicut for a period of 1 year starting from 1st July, 2005. Patients with previously diagnosed Type 2 Diabetes mellitus were randomly selected from among the inpatients of the department. The criteria used for the diagnosis of diabetes was fasting plasma glucose ≥ 126mg% or a 2 hour postprandial/OGTT plasma glucose ≥ 200mg% or symptoms of hyperglycemia and casual plasma glucose ≥200mg%. Type 2 diabetes mellitus was diagnosed on clinical grounds based on age of presentation, insulin requirements and after ruling out secondary causes. Those with Type 1 Diabetes Mellitus, secondary diabetes, overt renal failure, congestive cardiac failure, urinary tract infection or recent intercurrent illness were excluded from the study. All patients studied underwent,
A. Detailed assessment of history with stress on risk factors and atherosclerotic events.
B. Thorough general physical examination including anthropometric measurements and system examination for atherosclerotic vascular disease
C. Peripheral neuropathy was assessed by a detailed neurological examination and by monofilament.
D. For diabetic retinopathy, after adequate mydriasis a detailed fundus examination was done by a qualified ophthalmologist using a direct ophthalmoscope and diabetic retinopathy was graded as per the International classification of diabetic retinopathy and diabetic macular edema guidelines as follows:
  1. No retinopathy
  2. Mild non proliferative diabetic retinopathy
  3. Moderate non proliferative diabetic retinopathy
  4. Severe non proliferative diabetic retinopathy
  5. Early proliferative diabetic retinopathy
  6. High risk proliferative diabetic retinopathy

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7. Clinically significant macular oedema

E. 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 minimal respiration. Hip circumference was measured at the widest point between the hip and buttocks. Waist hip ratio (W/H ratio) was defined as waist circumference divided by the hip circumference. Cut off values for waist circumference were 90 cm and 80 cm 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.

F. Routine and special investigations including blood sugar, lipid profile, ECG, urine microalbumin-creatinine ratio and glycosylated hemoglobin were done. The fasting venous plasma glucose (FBS) and fasting lipid profile (FLP) were obtained after 12 hours of overnight fasting using the Olympus AU-400 Auto Analyzer and the 2 hour post prandial venous plasma glucose (PPBS) estimation was also done. The value of LDL was calculated using Freidewald’s formula when the triglyceride was more than 400mg/dl. Dyslipidemia was defined on National cholesterol education programme ATP 111 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 and more than or equal to 60mg/dl was considered high as per the ATP111 guidelines.

For urine albumin creatinine ratio, urinary tract infection was first ruled out by urine sediment analysis. The early morning spot urine sample was then sent for estimation of urine albumin creatinine ratio. Urine albumin estimation was based on the immunoturbidity due to the reaction between albumin and anti human albumin reagent and it was read at 340nm. Urine creatinine was estimated using Jaffe’s alkaline picate reaction. The urine albumin creatinine ratio was then calculated and graded as normal <30mg/g of creatinine; microalbuminuria – 30-299mg/g of creatinine and macroalbuminuria > ≥300mg/g of creatinine.

HbA1c was estimated by column chromatography method. The patients were categorized as those having a HbA1c of less than 8% which indicates good control of diabetes and those having more than 8% which indicates poor control of diabetes.

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

E. 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 value of ≤0.05 was 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 44 patients were studied of which 68% were males. The bias in the sex was in concordance with the admission statistics of the hospital. Only 20% of the study population had prior hypertension and all had blood pressure in the normal range during the course of study. The mean age of patients was 55.79 years. The mean duration of diabetes was 5-15 years. Though the waist circumference was normal in 50% of patients, 77.3% of patients had abnormally high waist-hip ratio.

The mean values of the various parameters expressed between the groups with a CIMT less than and more than 0.9 were calculated (Table1).

On comparing age with CIMT, no statistically significant association was obtained (p value:0.48). 54.5% had history or features suggestive of atheroembolic macrovascular disease at or during the study period. Retinopathy was present in 72.72% of patients. 81.81% 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 4 patients had demonstrable plaque by ultrasound. The proportion of patients with increased urinary albumin excretion rate increased in concordance with the duration of diabetes (63.63%, 86.36% and 90.9% in the <5 years, 5-15 years and ≥ 15 years groups respectively). As the urinary albumin excretion rate increased from normoalbuminuria to macroalbuminuria, an increase in the proportion of patients with increased carotid artery intima media thickness was observed ranging from 50% in normoalbuminuric group to 83.33% in macroalbuminuric group. On comparing retinopathy with albuminuria, p value was highly significant (p value= 0.0005), with all patients with macroalbuminuria having features of retinopathy (Figure 1). Among those with a duration of more than 15 years, 91% had increased carotid artery intima media thickness with a significant p value of 0.020 (Figure 2).
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p value: 0.07

Fig. 1 : Association of albuminuria with prevalence of retinopathy

p value: 0.06

Fig. 2 : Association of duration of diabetes with CIMT

p value: 0.06

Fig. 3 : Association of hypertension with CIMT

77.77% of those with hypertension had increased intima media thickness with a nearly significant p value of 0.06 (Figure 3). Though waist circumference and body mass index 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 4). 24 patients had previous atheroembolic events of which 66.66% had increased CIMT and the p value for this observation was statistically significant with a p value of 0.0148 (Figure 5). 76.47% of those with HbA1c>8% indicating poor control of diabetes had increased average intima media thickness (P value 0.0047) (Figure 5). All patients with HbA1c>8% had increased urine albumin excretion rate either in the microalbuminuric (64.70%) or in the macroalbuminuric (35.29%) range. Smoking and dyslipidemia was not found to have any association with intima media thickness.

The factors which were significant in univariate analysis were considered for multivariate analysis by multiple linear regression model. Among the various variables the maximum significance was obtained with waist hip ratio and evidence of atheroembolic disease with a p value of 0.062 and 0.070 respectively (Figure 6). The p value was only nearly significant (p value:0.07). 77.77% of those with hypertension had increased intima media thickness with a nearly significant p value of 0.06 (Figure 3). Though waist circumference and body mass index 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 4). 24 patients had previous atheroembolic events of which 66.66% had increased CIMT and the p value for this observation was statistically significant with a p value of 0.0148 (Figure 5). 76.47% of those with HbA1c>8% indicating poor control of diabetes had increased average intima media thickness (P value 0.0047) (Figure 5). All patients with HbA1c>8% had increased urine albumin excretion rate either in the microalbuminuric (64.70%) or in the macroalbuminuric (35.29%) range. Smoking and dyslipidemia was not found to have any association with intima media thickness.

The factors which were significant in univariate analysis were considered for multivariate analysis by multiple linear regression model. Among the various variables the maximum significance was obtained with waist hip ratio and evidence of atheroembolic disease with a p value of 0.062 and 0.070 respectively (Table 2) though the values did not attain statistical significance.

**Discussion**

Measurement of carotid artery intima media thickness by non invasive B mode ultrasonography can detect atherosclerosis
results were demonstrated by Gilles F.H Diercks et al\textsuperscript{15} whose study showed that urine albumin excretion is strongly related to subclinical atherosclerosis (assessed by IMT) in type 2 diabetic patients. 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\textsuperscript{16} 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. 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\textsuperscript{18} who observed that IMT correlated strongly with systolic blood pressure. 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\textsuperscript{17} observed that CCA IMT correlated strongly with HbA1c values. 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\textsuperscript{18} 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. On the other hand, Temelkova-Kurtktschiev et al\textsuperscript{19} noticed increased intima media thickness in diabetic patients with hyperlipidemia. Mohan Rema et al\textsuperscript{13} 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 CIMA on univariate analysis of which only waist hip ratio was found to be significant after multivariate linear regression analysis.

The present study revealed that the CIMA 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.\textsuperscript{20} An observation was made in this study that of the 24 patients who had atherosclerotic events, majority (66.67%) had intima

### Table 2: Multivariate Analysis

<table>
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<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>Std Error</th>
<th>F-test</th>
<th>P-Value</th>
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<td>Atheroembolic Disease</td>
<td>0.268</td>
<td>0.144</td>
<td>3.4704</td>
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<tr>
<td>Duration of Diabetes</td>
<td>0.062</td>
<td>0.161</td>
<td>0.1499</td>
<td>0.700881</td>
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<tr>
<td>HbA1c</td>
<td>0.051</td>
<td>0.060</td>
<td>0.7195</td>
<td>0.401906</td>
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<tr>
<td>Hypertension</td>
<td>0.194</td>
<td>0.180</td>
<td>1.1588</td>
<td>0.288868</td>
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<tr>
<td>Urine Albumin Creatinine Ratio</td>
<td>0.049</td>
<td>0.071</td>
<td>0.4789</td>
<td>0.493365</td>
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<tr>
<td>W/H Ratio</td>
<td>0.207</td>
<td>0.108</td>
<td>3.6954</td>
<td>0.062505</td>
</tr>
<tr>
<td>Constant</td>
<td>0.128</td>
<td>0.394</td>
<td>0.1051</td>
<td>0.747652</td>
</tr>
</tbody>
</table>

Females had a relatively lower value of CIMA 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\textsuperscript{10} who also observed significant higher IMT in men than women. In our present study no correlation was observed between age and intima media thickness. Doruk et al\textsuperscript{11} noticed that there was no significant correlation between age and carotid artery IMT. On the other hand Robin et al\textsuperscript{12} reported that IMT was independently and positively related to age. 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\textsuperscript{13} 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. Leena Mykannen et al\textsuperscript{14} in the Insulin Resistance Atherosclerosis Study reported that subjects with microalbuminuria had greater Common carotid artery IMT than those without microalbuminuria. Similar

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.\textsuperscript{7} Females had a relatively lower value of CIMA 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\textsuperscript{10} who also observed significant higher IMT in men than women. In our present study no correlation was observed between age and intima media thickness. Doruk et al\textsuperscript{11} noticed that there was no significant correlation between age and carotid artery IMT. On the other hand Robin et al\textsuperscript{12} reported that IMT was independently and positively related to age. 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\textsuperscript{13} 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. Leena Mykannen et al\textsuperscript{14} in the Insulin Resistance Atherosclerosis Study reported that subjects with microalbuminuria had greater Common carotid artery IMT than those without microalbuminuria. Similar at an early preclinical stage and help in the diagnosis of asymptomatic cardiovascular disease\textsuperscript{8} and whether increased CIMA 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.\textsuperscript{6} 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\textsuperscript{15} 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. On the other hand Saini et al\textsuperscript{16} noticed that microalbuminuria was more common in patients with longer duration of diabetes, a poor glycemic control. 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 to that of Masoud Manaviat et al\textsuperscript{7} who also reported increased prevalence of retinopathy in patients with microalbuminuria and macroalbuminuria. Masoud et al and Farhan et al\textsuperscript{18} had also noticed significant association between body mass index and retinopathy. 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.\textsuperscript{7} Females had a relatively lower value of CIMA 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\textsuperscript{10} who also observed significant higher IMT in men than women. In our present study no correlation was observed between age and intima media thickness. Doruk et al\textsuperscript{11} noticed that there was no significant correlation between age and carotid artery IMT. On the other hand Robin et al\textsuperscript{12} reported that IMT was independently and positively related to age. 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\textsuperscript{13} 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. Leena Mykannen et al\textsuperscript{14} in the Insulin Resistance Atherosclerosis Study reported that subjects with microalbuminuria had greater Common carotid artery IMT than those without microalbuminuria. Similar
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.

Conclusions

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. Our 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.

References