ORIGINAL ARTICLE

Correlation of Carotid Intimomedial Thickness with Coronary Risk Factors in Type 2 Diabetic Patients

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ABSTRACT

Aims: To compare the carotid intima-media thickness in type 2 diabetic patients with and without coronary artery disease (CAD), and to correlate the intima-media thickness (IMT) with known coronary risk factors. **Methods**: two hundred and twenty patients of type 2 diabetes were recruited for the study. History and physical examination were recorded. Laboratory investigations included fasting and 2-hour post-prandial blood sugar, blood urea, serum creatinine, lipid profile, glycated haemoglobin, and microalbuminuria. Ultrasonographic scanning of the carotid arteries was performed to measure the carotid IMT. For identification of cases of silent ischaemia, treadmill test (TMT) was performed. **Results**: The study group was divided into a non-CAD group (n=80), and a CAD group (n=140). The mean carotid IMT of the group as a whole, was 0.840±0.2 mm. The mean carotid IMT was significantly higher ($p<0.0001$) in type 2 diabetics with CAD (both overt and silent) than in those without CAD. In diabetics with CAD, the systolic blood pressure, diastolic blood pressure and triglycerides were found to be predictors of high mean carotid IMT. On subgroup analysis of the cases with silent ischaemia, the variables affecting carotid IMT were serum creatinine, total cholesterol, microalbuminuria/proteinuria, serum triglyceride levels, and diastolic blood pressure. **Conclusion**: A high carotid IMT is a surrogate and reliable marker of higher risk of CAD amongst type 2 diabetic patients, even in those without overt CAD. The study underlines the utility of carotid IMT as a simple, non-invasive, safe, and cheap screening test for the assessment of risk/prognosis of CAD in type 2 diabetics. We have also demonstrated the usefulness of measuring IMT, as a means to detect silent CAD among type 2 diabetics.

Key words: *Carotid intimomedial thickness, coronary risk factors, type 2 diabetes*

INTRODUCTION

Patients with diabetes mellitus suffer unduly from premature and severe atherosclerosis. The Framingham study[1] pointed out that diabetic individuals have higher serum concentrations of lipids and more hypertension, obesity, and thus are more prone to advanced atherosclerosis and it's sequelae, namely coronary artery disease (CAD), cerebrovascular disease, aortic atherosclerosis, and peripheral vascular disease. Coronary angiography (CAG) has been considered as the gold standard for the assessment of the degree of coronary atherosclerosis. But angiographic assessment of the coronary arteries is expensive, needs tertiary care hospitals and expertise and is not without risk.

Since atherosclerosis is a generalized phenomenon and is more or less present equally in the coronary, cerebral, and the carotid arteries; so, ultrasonographic assessment (carotid doppler) of easily accessible arteries has been advocated as a surrogate marker for less accessible vessels, such as coronary and cerebral arterial systems[2]. Ultrasound imaging, which can provide information on intima-media thickness (IMT), plaque presence and type, calcification, and wall diameter, offers the ability to examine pre-symptomatic lesions, assess atherosclerotic burden and hence the risk of cardiovascular events.

Noninvasive screening procedures/investigations are valuable in identifying diabetic patients at risk for CAD. In clinical settings, this can potentially lead to early interventions. The cardiovascular health study collaborative research group[3] has recently observed, in 4476 subjects without clinical cardiovascular disease followed over 6 years, that the relative risk for myocardial infarction (MI) or stroke for the quantile with the highest IMT as compared with the lowest quantile was 3.87. IMT is a strong independent predictor for new cardiovascular events, even after statistical adjustment for other traditional risk factors. In a case control study of 772 persons selected from the ARIC population to evaluate adults free of clinical cardiovascular disease, thickness, had consistently higher values for atherogenic risk factors (age, body mass index, systolic and diastolic blood pressure, pack years of smoking, total triglycerides, low-density lipoprotein (LDL cholesterol), and low high density lipoprotein (HDL cholesterol) than control subjects[4]. Carotid IMT (CIMT) has been shown to be independently associated with CAD in Indian subjects[5].

There are few Indian studies where carotid intimal-medial thickness has been measured in type 2 diabetics. Therefore, the present study was planned to generate more data on this

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subject with the aims of measuring the carotid IMT in type 2 diabetics, with or without CAD, and to correlate carotid IMT with various known coronary risk factors.

MATERIAL AND METHODS

two hundred and twenty patients, who were already under treatment for diabetes mellitus at Nepalganj medical college and teaching hospital, Kohalpur were included in the present study. All the cases were evaluated as outpatient in the Department of Medicine over a period of 2 years from July 2006 to June 2008. The cases were selected after satisfying all the exclusion/ inclusion criteria and consisted of consecutive selected cases. Only patients of type 2 diabetes above the age of 35 years were included. Presence or past history of gross congestive cardiac failure, renal disease, thyroid disease, hepatic disease, diabetic ketosis, stroke, and associated rheumatoid disease were criteria for non-inclusion to the study. All patients gave informed consent to participate in the study, and the study protocol was duly approved by the ethical committee of the hospital.

A detailed history and physical examination were recorded, with emphasis on brachial blood pressure, height, weight, waist-hip ratio, and fundoscopy. Laboratory investigations included fasting and 2 hour post-prandial blood sugar, blood urea, serum creatinine, lipid profile (total cholesterol, LDL, HDL, VLDL, and triglycerides). Glycated haemoglobin (HbAIC) was determined quantitatively using the glycated haemoglobin kit in whole blood.

Microalbuminuria (MAU) was determined by an immunoturbidimetric assay. Ultrasonographic scanning of the carotid arteries was performed on the Ge Vivid3 equipped with colour flow imaging and pulse Doppler, with an electrical linear transducer (mid frequency of 7.5 MHz). The scanning session lasted for an average of 30 minutes. The IMT, as defined by Pignoli et al,[6] was measured as the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line. The first line represents the lumen intimal interface and the second line is produced by the collagen containing upper layer of the tunica adventitia. The image was focussed on the posterior far wall and four images of the left and right common carotid arteries each were recorded at least 15 mm proximal to the bifurcation. The CIMT was calculated as the mean of eight measurements.

IMT values below 0.8 mm were considered as normal. The presence of plaques and degree of stenosis was noted and analysed. Plaque was defined as a localized lesion of thickness ≥1.0 mm; stenosis was defined as > 50% occlusion with systolic frequency peak ≥ 4.0 KHz and spectral broadening. For identification of CAD, history of angina/MI, 12 lead electrocardiogram, TMT, 2D echocardiography, and coronary angiography etc. were performed as and when needed. The diabetics were subgrouped, according to the presence or absence of CAD into two groups.

(I) CAD Group

Overt ischaemia: Presence of CAD, as suggested by history of previously known angina or infarction, or affirmative response to the Rose questionnaire and/or ECG suggestive of probable myocardial infarction or possible myocardial ischaemia by Minnesota codes - 1-1, 1-2 (Q wave), 4-1-1 (ST segment depression); 5-1 (T-wave inversion); 9-2 (ST segment elevation). Silent ischaemia: Those diabetics without overt CAD were subjected to a stress test (Treadmill test) according to Bruce protocol and those having a positive test result were labelled as having silent ischaemia and those with a negative result were labelled as non-CAD patients. Those cases with an inconclusive result of the test were excluded from the study.

(II) Non - CAD Group - those diabetics without overt or silent CAD.

Data Analysis

Cases were analysed by dividing them into 3 groups, i.e., (i) type 2 diabetics without CAD (group I), (ii) type 2 diabetic patients with CAD, overt or silent (group II) and, (iii) type 2 diabetics with silent CAD (group IIb). Data was expressed as mean±SD. All relevant details including history, investigations, etc., were listed in the proforma and further analysed. The continuous data variables were tested for statistical significance of the difference between two population means by using the student's't' test and Mann-Whitney test. Pearson's correlation coefficient was calculated between independent variables in all groups. Multivariate regression analysis was computed with the SPSS statistical software package and p values < 0.05 were considered significant.

RESULTS

A total of two hundred and twenty (220) cases of type 2 diabetes were recruited to the study (130 males and 90 females). The patients were subdivided into two groups.

(1) Group I - Non-CAD (n=80), which comprised of 50 males and 30 females.
(2) Group II - CAD, (n= 140), which comprised of 80 males and 60 females.

A sub-group of 30 patients with silent ischaemia (group IIb) was made from group II. The characteristics of all the subjects and of the two groups separately are shown in table I

The left-sided CIMT in the whole group was significantly ($p<0.05$) correlated to the age of cases, blood urea and to the right-sided and mean CIMT. Amongst group I cases, the left-sided CIMT was significantly ($p<0.05$) correlated to rightsided CIMT, mean CIMT, blood urea, glycated haemoglobin and, duration of diabetes.

Variable	Whole Group Mean±SD	Group I Non-CAD Cases	Group II CAD Cases
Age (years)	59.78±8.81	57.08±8.64	61.31±8.64
Duration of Diabetes (years)	11.23±6.89	11.40±6.85	11.14±6.96
Weight (kg)	67.12±11.90	66.13±12.67	67.68±11.50
Height (cm)	161.43±10.56	162.82±11.24	160.65±10.16
BMI (kg/m^2)	26.40±10.56	25.68±4.16	26.80±3.85
WHR	.9701±0.0720	0.9701±0.0720	0.9709±0.0728
SBP (mmHg)	140.07±15.28	139.90±15.16	140.17±15.46
DPB (mmHg)	86.67±10.45	87.55±8.52	86.17±11.43
FBS (mg%)	133.20±42.98	136.45±50.18	131.37±38.61
PPBS (mg%)	183.31±63.51	186.95±73.24	181.25±57.77
Urea (mg%)	33.22±11.28	31.27±10.17	34.32±11.79
Creatinine (mg%)	1.02±0.28	.96±.22	1.05±0.31
HbA1c (%)	7.64±1.42	7.43±1.436	7.75±1.42
Total cho.l (mg%)	182.08±41.61	173.28±38.91	187.04±42.52
LDL cho.l (mg%)	110.16±34.69	106.21±29.74	112.39±37.20
HDL cho.l (mg%)	42.46±9.00	44.18±9.26	41.49±8.77
VLDL cho.l (mg%)	29.94±16.16	26.73±14.14	31.76±17.02
Triglyceride (mg%)	155.17±82.57	142.38±73.33	162.38±87.02
Microalbuminuria/ Proteinuria (mg/g creatinine)	131.68±438.0	71.20±185.0	165.76±529.0
Left CIMT (mm)	0.840±0.20	0.749±0.20	0.891±0.18
Right CIMT (mm)	0.842±0.20	0.759±0.20	0.906±0.215
Mean CIMT (mm)	0.840±0.20	0.755±0.17	0.891±.198

BMI - Body mass index, WHR - Waist hip ratio, SBP - Systolic blood pressure, DBP - Diastolic blood pressure, FBS - Fasting blood sugar, PPBS - Post prandial blood sugar, CIMT - Carotid intima - media thickness

Table I: Characteristics of study patients

Characteristics	Group	Mean±SD	p value	
			Student's t test	Mann Whitney test
Microalbuminuria/ Proteinuria	Group II	165.7606±529.1166	0.278	0.019
	Group I	71.2000±185.7156		
Left sided CIMT	Group II	0.891±0.18	0.0001	0.0001
	Group I	0.749±0.20		
Right sided CIMT	Group II	0.906±0.215	0.05	0.0001
	Group I	0.759±0.20		
Mean CIMT	Group II	0.891±0.198	0.0001	0.001
	Group I	0.755±0.171		

CIMT - Carotid intima - media thickness

Table II: Comparison of both the groups

In Group II, the left- sided CIMT had a highly significant (p<0.01) correlation with the mean CIMT and right-sided CIMT. The right-sided CIMT in the whole group was significantly correlated to the age of cases (p<0.05), and left- and mean CIMT (p<0.01 each). Amongst group I cases, the right-sided CIMT was significantly (p<0.05) correlated to left-sided CIMT, mean CIMT and, the age of cases. In-group II, the right-sided CIMT had a highly significant (p<0.01) correlation with mean and left-sided CIMT.

As seen in Table II, mean CIMT as well as left and right sided CIMT were significantly higher (p<0.0001) in type 2 diabetics with CAD, than in those without CAD. In group I, on multivariate regression analysis, serum to be the strongest predictors of higher than normal CIMT (p<0.041 and p<0.05 respectively) (Table III). On step-wise regression, duration of diabetes was identified as another predictor, with p<0.002. On multivariate regression analysis in group II, keeping the mean CIMT as the dependent variable, the systolic blood pressure (SBP), diastolic blood pressure (DBP) and triglycerides (TG) were found to be predictors of higher than normal mean CIMT (p<0.050, 0.017 and 0.010 respectively) (Table III), triglyceride level being the most remarkable.

Statistical cross tabulation revealed that mean CIMT was normal (≤ 0.8 mm) in 36.7% of CAD patients as compared to 62.5% of non-CAD patients. Whereas, 63.3% of type 2 diabetic patients with CAD had a mean CIMT > 0.8 mm, as compared to only 37.5% of non-CAD patients (p<0.01). Statistical cross tabulation of constant variables revealed that 66.2% of CAD cases had plaque occurrence as compared to 35% of non-CAD cases. 33.8% of the CAD cases did not have plaques, as compared to 65% of non-CAD cases (p<0.003).

This finding indicates that presence of plaques is strongly and significantly associated with the prevalence of CAD. Degree of stenosis was not associated with the prevalence of CAD. The cases demonstrating silent ischemia (group IIb) were also analysed separately. There were 60 patients in this subgroup of CAD cases, with CIMT of 0.880±0.19 mm (range 0.49-1.33 mm). The mean CIMT being the dependent variable, multivariate regression analysis (Table III) showed that the variables affecting mean CIMT in this subgroup of silent ischemia cases were serum creatinine, total cholesterol, and microalbuminuria/proteinuria (p<0.05). Also, a highly significant effect on mean CIMT was observed to be that of serum triglyceride levels (p<0.001). Upon step-wise regression analysis diastolic blood pressure, was identified as another variable affecting mean CIMT (p<0.05).

Predictor	Total	Group I non CAD	Group II CAD	Group IIb TMT positive
Age	.084	.314	.879	.231
Duration of diabetes	.975	.173	.621	.090
Duration of hypertension	.525	.990	.446	.080
Weight	.967	.347	.216	.445
Height	.652	.216	.401	.452
BMI	.993	.349	.267	.527
WHR	.836	.902	.351	.180
SBP	.413	.642	.050	.103
DBP	.087	.386	.017	.528
FBS	.250	.651	.188	.956
PPBS	.144	.550	.361	.277
Urea	.578	.368	.573	.527
Creatinine	.404	.041	.766	.050
Uric acid	.154	.203	.905	.132
Glycated Hb	.726	.809	.799	.733
Total chol.	.537	.975	.547	0.050
LDL chol.	.740	.657	.472	0.067
HDL chol.	.865	.953	.630	.164
VLDL chol	.940	.852	.905	.259
TG	.125	.957	.010	.006
Microalbuminuria/ Proteinurea	.320	0.050	.846	0.050

Table III: Regression analysis (annova) Dependant variable: mean cimt

DISCUSSION

Intima-media thickness of the common carotid artery is considered to be an excellent non-invasive measure of generalized atherosclerosis[7,8,9,10,11] and also a surrogate marker of coronary artery disease[12,13]. It is also extensively used to examine the stage of atherosclerosis and to evaluate the regression of atherosclerotic lesions following intervention therapies[14-16]. The international atherosclerosis project has suggested that the carotid and cerebral arteries and the aorta undergo the atherosclerotic process approximately at the same age as the coronary arteries[17]. Moreover, there is good agreement between histological examination and the ultrasonographic evaluation of the carotid arteries[18]. Mohan et al[19] in the Chennai Urban Population Study (CUPS) in 2000 studied IMT of the carotid artery in South Indian diabetic and nondiabetic subjects and observed that the mean IMT value of the diabetic subjects (0.95±0.31 mm) was significantly higher than those of the non-diabetic subjects (0.74±0.14 mm) ($p<0.001$). Both in the normal and diabetic subjects, these values increased with age.

At any given age, the diabetic subjects had higher values than the non-diabetic subjects but the difference reached statistical significance after the age of 50 years ($p<0.05$). IMT showed a correlation with age and duration of diabetes in the diabetic subjects. Multivariate regression analysis showed that age and diabetes were the major risk factors for IMT. Kawamori et al[9] (1992) in their study on the prevalence of carotid atherosclerosis in diabetic subjects concluded that IMT is linearly related with age in diabetic subjects (IMT = [0.0155 x age] + 0.32450). Multivariate regression analysis of 275 type 2 diabetic cases indicated that smoking, hyperlipidaemia, duration of diabetes, hypertension and age were factors determining thickness of the carotid arterial wall.

The mean CIMT in our study group of a total of 220 cases with type 2 diabetes was 0.840 ± 0.18 mm. This is lower than the value reported by Mohan et al in the CUPS study (0.95 ± 0.31 mm), yet higher than normal. The reason for this seems to be the fact that 67% of the cases in the CUPS study were newly diagnosed case of diabetes and therefore may not be receiving statins or glitazones. On the contrary, in our study the mean duration of diabetes was 11.23 years, and most of our patients were already on these drugs, which are known to decrease atherosclerosis and thereby CIMT.

In a study in 2001 by Jadhav et al,[20] an IMT greater than 0.8 mm was observed in CAD patients (whether diabetic only, hepertensive only, or both), as against those without CAD; this difference was most marked in the hypertensive group (22.2% vs. 3.6%) and contributed to the increased arterial thickness in diabetics with concomitant hypertension. Multivariate regression analysis revealed CIMT to be associated with CAD with an odds ratio of 2.40. This fact was reinforced by our study wherein CIMT was found to be very strongly and significantly correlated with the prevalence of CAD ($p<0.0001$). In our study, among the CAD patients, hypertriglyceridaemia (HTG) was significantly correlated to mean CIMT ($p<0.001$). Chen et al[22] investigated the association of fasting and postprandial triglyceride levels with CIMT among type 2 diabetic patients in Southeast China. The CIMT in patients with postprandial HTG was significantly greater than that in patients with postprandial normo-triglyceridaemia ($p<0.05$). Nagai et al,[23] in 1998, compared CIMT in asymptomatic older subjects with exercise - induced myocardial ischaemia.

They observed that exercise induced ST-segment depression was associated with increased IMT ($p<0.0001$) independent of age and manifest CAD. After adjustment for age, IMT values progressively increased from healthy subjects to asymptomatic subjects with positive exercise ECG alone to those with concordant positive ECG and thallium scintigraphic findings who had virtually identical IMT to subjects with manifest CAD. Each 0.1 mm increase in IMT was associated with a 1.91 fold increased risk for concordant positive exercise tests or manifest CAD, independent of other significant predictors of CAD. We have also found a strong and significant correlation between mean CIMT and prevalence of silent ischaemia, ($p<0.001$). On multivariate regression analysis, keeping mean CIMT as the dependent variable, the predictors that were seen to affect IMT included serum creatinine, total cholesterol levels, serum triglyceride levels and microalbuminuria. Jadhav et al[24] in their study on association of microalbuminuria with IMT and CAD observed that microalbuminuria had a strong association with high IMT in diabetic subjects. Our results in diabetics with silent ischemia are similar to their observations, as microalbuminuria had a significant correlation ($p<0.05$) with IMT in this subgroup.

CONCLUSION

The present study comprised of 220 patients with type 2 diabetes (130 males and 90 females). A high mean CIMT (>0.8 mm) was seen in 54% of the cases. Approximately 2/3rd (63.3%) of the total 140 diabetic patients with CAD had high IMT, but in the 80 non-CAD cases only 1/3rd (37.5%) had high IMT values. Comparison of type 2 diabetic patients with and without CAD revealed that the presence of CAD was significantly associated with age ($p<0.014$), microalbuminuria ($p<0.019$), and mean CIMT ($p<0.0001$). Sub-group analysis of silent ischaemia (TMT positive) cases revealed almost similar findings. Thus, we may conclude that CIMT is higher in type 2 diabetics with CAD (both overt and silent) as compared to diabetics without CAD. In asymptomatic type 2 diabetic patients, measurement of CIMT is a simple and safer alternative to stress testing for detection of silent CAD. Also, as CIMT lends itself conveniently for measurement, it can be utilized as a surrogate marker of CAD. It cannot replace coronary angiography in the assessment of risk/prognosis of CAD but it can help the clinician decide which diabetic is at higher risk for CAD and hence may benefit from coronary angiography.

Psychosocial Stressors	Male (N=18)	Female (N=47)	Total (N=65)
No stress	0 (0.00%)	0 (0.00%)	0 (0.00%)
Negative childhood events	0 (0.00%)	0 (0.00%)	0 (0.00%)
Family history of morbidity and disability	2 (11.11%)	5 (10.64%)	7 (10.77%)
Lifestyle and life management difficulties	0 (0.00%)	0 (0.00%)	0 (0.00%)
Education and literacy related problems	14 (77.78%)	38 (80.85%)	52 (80.00%)
Primary support group including family circumstances and conflict	3 (16.67%)	14 (29.78%)	17 (26.15%)
Social and environmental problems	8 (44.44%)	5 (10.64%)	13 (20.00%)
Housing or economic hardships	2 (11.11%)	4 (8.51%)	6 (9.23%)
Physical environment	0 (0.00%)	0 (0.00%)	0 (0.00%)
Other psychosocial circumstances	1 (5.56%)	3 (6.38%)	4 (6.15%)
Legal	0 (0.00%)	0 (0.00%)	0 (0.00%)

Table II: Types of Psychosocial Stressors

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