Original Article

Association of Common Carotid Intimal Medial Thickness (CCA-IMT) with risk factors of atherosclerosis in patients with type 2 diabetes mellitus

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Abstract

Objective: To determine the association of Common Carotid Intimal Medial Thickness (CCA-IMT) with risk factors of atherosclerosis in patients with type 2 diabetes mellitus.

Methods: This is an observational study carried out in 200 type 2 diabetic patients. Age, gender, duration of diabetes, history of ischaemic heart disease, hypertension and smoking was recorded. Body mass index, glycosylated haemoglobin (HbA1c), total cholesterol, triglyceride and high density (HDL) cholesterol were determined in all the patients. CCA-IMT determination was done by Carotid Doppler Ultrasonography.

Results: There were 120 (60%) males and 80 females (40%). Ages ranged from 28 to 79, mean 59.5 ± 9.07 years. IMT on right side ranged from 0.4mm to 2.4 mm, mean 0.88mm and on left side mean IMT was 0.93mm, range 0.5mm to 2.5mm. Duration of DM and BMI were correlated with IMT on both the sides ($p<.05$), statistically inverse correlation was seen with HDL cholesterol ($p<.05$). No significant correlation was seen with other variables.

Conclusion: Duration of DM, BMI and HDL cholesterol were associated with CCA-IMT in patients with type 2 DM. No significant association was seen with other risk factors (JPMA 59:590; 2009).

Introduction

Atherosclerosis is the underlying disease process leading to ischaemic heart disease (IHD), cerebrovascular accidents and peripheral vascular diseases.[1] It is the leading cause of morbidity and mortality all over the world. It is a slowly progressive disease with multiple risk factors. Modifiable risk factors include diabetes mellitus (DM), fatty diet, hypercholesterolaemia, hypertension and smoking.[2] Non modifiable risk factors are male gender, race and family history. Increase in common carotid intimal medial thickness (CCA-IMT) and carotid stenosis secondary to carotid plaque (CP) are markers of atherosclerosis. Its early detection helps to identify individuals at risk.[3] High-resolution B-mode imaging of the carotid artery IMT has been shown to reflect histopathologically verified atherosclerosis and is therefore widely used to detect and quantify noninvasive measurements of atherosclerosis.[4] CCA-IMT is associated with all the subtypes of ischaemic stroke, carotid plaque, and cardiovascular deaths.[5] Studies have shown a fair but not a strong correlation of carotid IMT with angiographically verified coronary artery disease.[6]

Different groups have performed measurements at different sites of carotid artery and it has been shown that CCA-IMT is a good predictor of stroke incidence, whereas internal carotid artery (ICA) IMT measurement has a greater power of prediction for myocardial infarction.[7] CCA-IMT has been shown to slow down or even regress with control of blood pressure, antihyperlipidaemic drugs and multifactorial interventions in diabetic patients.[8] Diabetes mellitus is itself a powerful independent risk factor of carotid atherosclerosis.[9]

There are conflicting reports in the literature regarding the association of CCA-IMT with risk factors of carotid atherosclerosis. Geroulakos G et al[10] and Kanters SD[11] were unable to find statistical significant correlation of CCA-IMT with age, gender, duration of DM, serum total cholesterol and triglyceride levels in patients with type 2 diabetes mellitus. Others have reported an association between CCA-IMT with risk factors of atherosclerosis.[3,12] Considering the variability in the findings of different studies, further research is required to find the main determinants of carotid atherosclerosis.

The present study was done to determine the association of common carotid artery intimal medial thickness with multiple risk factors of atherosclerosis among patients with type 2 diabetes mellitus by performing high resolution carotid doppler ultrasonography.

Patients and Methods

The study was conducted at the Combined Military Hospital, Lahore, from 01 December 2007 to 31 May 2008. All patients with type 2 diabetes mellitus (DM) reporting to the department of internal medicine were consecutively enrolled in the study, after taking consent. Age, gender, body mass index (BMI), history of hypertension, Ischaemic Heart Disease (IHD),

smoking and duration of DM were recorded. Haemoglobin A1c, triglyceride, total cholesterol and HDL cholesterol were checked in all the patients. Carotid intimal medial thickness was measured by Doppler ultrasonography. Body mass index was calculated as weight in kilograms divided by height in meters squared. Glycosylated haemoglobin was measured with liquid cation exchange chromatography (Pharmacia). Total cholesterol, HDL cholesterol, and triglyceride levels were measured using enzymatic assays (Boehringer Mannheim, Diagnostica Mannheim, Mannheim, Germany).

CCA-IMT Ultrasonographic Measurements

Ultrasound study was performed in a standard manner by an examiner who was specifically trained in the procedure. All sonograms were obtained with the patient in the supine position and the head turned slightly to the contralateral side. A Biosound Phase Two ultrasound device equipped with a 10-MHz annular array probe was used. Video-recorded examinations were quantitatively analyzed using a computer-assisted reading procedure.[13] The high-resolution B-mode ultrasonographic imaging was performed to ensure the valid and reliable identification of carotid arterial intimal thickness.

Data was fed into SPSS version 13. Pearson and Spearman's correlation coefficients were applied for determining association of different risk factors with CCA-IMT. The level of significance was determined by P<.05.

Results

There were 200 patients, 120 (60%) males and 80 (40%) females; age range was 28 to 79 years, mean 59.5 ± 9.07 years. Patients were divided in four age groups. The majority of patients 89 (44.5%) were between the age range of 61 to 70 years while only 11 (5.5%) patients were beyond the age of 70 years. Similarly results of other variables according to stratification have been shown in Table-1.

There was no significant statistical difference between the two common carotids IMT (p < .08). Fair association was seen with duration of DM, and BMI while inverse correlation was seen with HDL Cholesterol levels. For duration of DM pearson coefficient for right and left common carotids were 0.29 and 0.18 respectively; and for BMI pearson coefficient for right and left CCA IMT were 0.17 and 0.27 respectively. For HDL cholesterol inverse pearson correlation of 0.23 for right and 0.14 for the left was found.

Further statistical analysis was done among different groups of each category of risk factors which reveals that mean CCA-IMT was 0.91mm, 0.87mm, 0.92mm and 0.98mm among the age groups of ≤ 49 years, 50 to 60 years, 61 to 70 years and ≥ 70 years respectively. Pearsons correlation coefficient was 0.65 with p value of 0.03 among the patients beyond 70 years of age and was found to strongly correlate with CCA-IMT, though the number of patients were only 11.

Table-1: Characteristics of Patients.

Parameters	No of Patients (%)
Age (years)	
≤ 49	26(13%)
50-60	74(37%)
61-70	89(44.5)%
≥71	11(5.5%)
Gender	
Male	120(60%)
Female	80(40%)
HbA1c(%)	
≤6	162(81%)
>6	38(19%)
Cholesterol	
≤200mg/dl	115(57.5%)
>200mg/dl	85(42.5%)
Triglyceride	
≤196mg/dl	120(60%)
>196mg/dl	80(40%)
HDLCholesterol	
≤39mg/dl	161(80.5%)
>39mg/dl	39(19.5%)
BMI(kg/m2)	
≤25	61(30.5%)
25.1-30	103(51.5%)
>30	36(18%)
CCA-IMT(Mean)	
≤1mm	147(73.5%)
>1mm	53(26.5%)
HistoryofSmoking	
Present	19(9.5%)
Absent	181(90.5%)
HistoryofHypertension	
Present	111(55.5%)
Absent	89(44.5%)
HistoryofIHD	
Present	44(22%)
Absent	156(78%)

HBA1c= glycosylated hemoglobin, HDL=high density lipoprotein, BMI=body mass index, CCA-IMT= Common Carotid Intimal medial thickness, IHD=Ischemic Heart Disease.

Table- 2: Descriptive Characteristics of Patients.

Variables	N	Min	Max	Mean	SD
Age (years)	200	28	79	59.53	9.1
Duration of DM (years)	200	.1	19.0	6.931	3.8
HbA1c (%)	200	3.9	9.5	5.630	.74
Cholesterol (mg/dl)	200	81.2	282.2	19.7	30.5
Triglyceride (mg/dl)	200	71.2	312	89.5	89
HDL (mg/dl)	200	23.4	70.2	39.6	9.36
BMI (kg/m2)	200	16.0	46.9	26.728	5.02
IMT-RT (mm)	200	0.4	2.4	0.881	0.28
IMT-LT (mm)	200	0.5	2.5	0.932	0.28

N=total no of patients, HBA1c= glycosylated hemoglobin, HDL=high density lipoprotein, BMI=body mass index, IMT-RT= intimal medial thickness right, IMT-LT= intimal medial thickness left, SD= standard deviation.

Table-3: Correlation of Risk Factors with Common Carotid Intimal- Medial Thickness.

Variables	IMT(RT)		IMT(LT)	
	Correlation Coefficient	p value	Correlation Coefficient	p value
AGE (Years)	.10	.14	0.04	.56
SEX*	.01	.86	.02	.72
DURATION OF DM	.29	<.01	.18	.01
CHOLESTEROL (mg/dl)	.10	.14	.02	.71
TRIGLYCERIDE (mg/dl)	.10	.14	.05	.43
HDL (mg/dl)	-.23	.001	-.14	.04
BMI (Kg/M2)	.17	.01	.24	.001
Hba1c	.01	.81	.01	.79
SMOKING*	.09	.17	.004	.95
HTN*	.09	.16	.08	.23
IHD*	.03	.58	.04	.55

Correlation coefficient has been determined by Pearson and Spearmen* method where ever appropriate, p value <.05 is considered significant.

No significant correlation was found among the three age groups younger than 70 years. Mean IMT in males and females were 0.90mm and 0.91mm respectively. Duration of DM was subdivided into two groups and correlation was done with CCA-IMT. Pearson correlation of 0.47 was found to be strongly correlated in the group having duration of DM of more than 6.9 years. Among the three BMI groups the strongest correlation was present among those patients having BMI > 30 (pearson correlation coefficient = 0.62). When the association of other risk factors in a particular stratified group was determined then no statistically significant correlation was found with sex, HbA1c, total cholesterol, triglyceride levels, history of hypertension, ischaemic heart disease and smoking as shown in Tables-2&3.

Discussion

This study shows modest association of CCA-IMT with duration of DM and BMI, whereas inverse correlation was seen with HDL cholesterol. This is in conformation with a number of previous studies.[9,12-15] However our results are conflicting with Frost d[12] who also reported correlation of CCA-IMT with age, cholesterol level and with the history of hypertension. Although our results reveal that there is a correlation of CCA-IMT with age among patients older than 70 years, the number of patients in this age bracket is so small that it cannot be given significance and requires further research with more patients in this age group.

Bonora et al[9] found that CCA-IMT was increased in diabetic patients as compared to controls and increased central obesity reflected by increased waist to hip ratio was an independent risk factor for carotid atherosclerosis. Similarly Faeh et al[16] found that increased adiposity and other risk factors start playing a pivotal role in the genesis of carotid atherosclerosis even in patients with impaired glucose tolerance. Wagenknecht LE[14] showed duration of diabetes directly affects the CCA-IMT and he also found that chronic hyperglycaemia was an independent risk factor for carotid atherosclerosis. It has also been observed that relatives of type 2 diabetic patients are prone to have increased CCA-IMT and it is hypothesized that this may be due to altered metabolic state characteristic of DM before florid expression of hyperglycaemia.[14] Kong et al[17] found that CCA-IMT was closely associated with age, male sex and smoking. In our study we could not find such an association. This is understandable as protective factor of female gender on premature atherosclerosis is lost in diabetic patients.[18] We confirm the findings of Yang et al[19] who did not see any difference in CCA-IMT in the two carotids.

Taniguchi et al[20] found a strong association of age, duration of DM and raised non esterified free fatty acids while no correlation was seen with BMI and raised cholesterol or triglyceride levels. Ciccone M et al,[21] Naya T et al[22] and Poredos P[23] found that CCA-IMT was correlated with smoking and body mass index, in contrast Leo Niskanen et al[15] found no association of CCA-IMT with history of smoking or hypertension. In their study the main determinants of IMT in NIDDM patients were post glucose insulin levels and abnormal lipoprotein profiles characteristic of NIDDM and insulin resistance syndrome.

Similar to our observation Ciccone et al[21] found that BMI is strongly and independently associated with the IMT of common carotid artery. Their results suggest that central fat accumulation may accelerate the development of earlier clinically silent stages of atherosclerosis, thus possibly explaining the higher prevalence of cardiovascular diseases in patients with abdominal obesity. Naya et al[22] found smokers with high body mass index, high fasting serum insulin, or high systolic blood pressure to have larger CCA-IMT values than would be predicted by consideration solely of the individual risk factors. They also found that Diabetes mellitus status itself and even impaired glucose tolerance as compared to normal glucose tolerance is a strong predictor of CCA-IMT. The results of Poredos et al[23] show that smoking is associated with dose-related impairment of FMD (flow mediated dilation) and increased IMT of the carotid arteries. Impairment of FMD

occurs in smokers very early and is the earliest detectable event, preceding morphologic changes of the vessel wall and some harmful effects of smoking on the vessel wall are gender related.[23]

Temelkova et al[24] found that once age and sex is adjusted CCA-IMT is strongly correlated with triglyceride levels and total to HDL cholesterol ratio but we did not find such correlation with either cholesterol or triglyceride levels in our study. No independent determinant of IMT was found in the diabetic group by multivariate analysis in Temelkovo study.[24] They concluded that newly detected type 2 diabetic patients exhibit a higher degree of early atherosclerosis than normal glucose-tolerant subjects matched for age and sex. Their data suggested that hyperglycaemia, together with a clustering of risk factors, and in particular dyslipidaemia, may cause intimal-medial thickening in the early phases of diabetes.

It is well established that in non diabetics age, gender, total cholesterol and smoking are independent determinants of CCA-IMT.[25] Irrespective of well known risk factors of atherosclerosis Geroulakos G et al[10] and Kanters SD[11] were unable to found any statistical significant correlation between CCA-IMT with age, gender, duration of DM, serum total cholesterol and triglyceride levels in patients with type 2 diabetes mellitus. It is probably explained by the fact that diabetes itself is of crucial importance for the development of atherosclerosis because of clustering of multiple interrelated metabolic disturbances that it over shadows the contribution of other risk factors. In our study also majority of patients had other risk factors in addition to diabetes mellitus.

In conclusion our data shows that CCA-IMT is directly associated with duration of DM and BMI while inverse correlation has been seen with HDL cholesterol. No correlation was observed with age, gender, levels of cholesterol, triglyceride, HbA1c, history of smoking, hypertension and ischaemic heart disease. Considering the conflicting outcomes of different studies it is suggested that further research is required in larger number of patients to find out the interrelationship and contribution of various risk factors of carotid atherosclerosis in diabetic patients.

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