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DIABETES MELLITUS;
CAROTID THICKNESS - ASSOCIATION OF GLYCEMIC CONTROL

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Statement of Novelty: CIMT and Type 2 Diabetes Mellitus

ABSTRACT: Diabetes mellitus is a modifiable risk factor for generalized atherosclerosis. Measurement of carotid intima media thickness by Doppler ultrasonography can be used to measure the extent of atherosclerosis. **Objectives:** To determine the association of carotid atherosclerosis in patients with type 2 diabetes mellitus and its relationship with glycemic control. **Study Design:** Cross-sectional comparative study. **Period:** 12 months June 2015 to May 2016. **Setting:** Creek General Hospital in the Department of Medicine and Radiology, Karachi, Pakistan. **Method:** The subjects were selected from diabetic patients presenting to the Out-Patient Department and controls from their attendants. All subjects had a detailed history, physical examination and laboratory investigations recorded. The variables included age, gender, weight, BMI, blood pressures, fasting and post prandial blood sugars, HbA1c and lipid profile. All individuals underwent B-mode ultrasound for carotid Doppler studies. A single operator conducted all the Doppler studies. The carotid intima media thickness was measured and the presence of carotid plaque was recorded for each subject. The data was entered on SPSS ver 20.0. Numbers and percentages were calculated for categorical data while mean±standard deviation was calculated for continuous data. The carotid intima media thickness and its association with diabetes were analyzed by Student's t test. P-value of <0.05 was considered significant. Among the diabetic patients the relationship of glycemic control and carotid intima media thickness was analyzed through student's t-test. P-value of <0.05 was considered significant. The association of presence of carotid plaque for diabetic and non-diabetic subjects was assessed by Chi-square test. P-value of <0.05 was taken as significant. Association of carotid plaque among diabetic patients with satisfactory and unsatisfactory glycemic control was also assessed through the Chi-square test and p-value of<0.05 was considered significant. **Result:** Out of the total study population of 237 subjects, which consisted of 119 diabetic and 118 normal controls, there were 105 male and 132 female patients. The mean fasting blood sugar was 113.3±55.2 mg/dl, mean random blood sugar was 185.9±102.0 mg/dl, mean HbA1c was 6.98±2.5 %. Mean ±SD of carotid intima media thickness was 0.91±0.17 mm. Results revealed that diabetes has significant association with the thickness of carotid intima media (p-value<0.000). A total of 28 individuals (11.8%) had a carotid intima media thickness that was classified as a localized carotid artery plaque. The presence of carotid plaque also showed a significant association with the presence of diabetes. The degree of glycemic control showed no relationship with carotid intima media thickness. The presence of carotid plaque also showed no association with degree of glycemic control. **Conclusion:** CIMT measured by Doppler ultrasonography was found to be significantly associated with the presence of diabetes mellitus. There was no relationship of glycemic control with CIMT among the diabetic patients.

Key words: Doppler ultrasound, carotid intima-media thickness, CIMT, atherosclerosis, type 2 diabetes mellitus, glycemic control.

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INTRODUCTION

Global cardiovascular mortality has increased by around 41.7% in the period from 1990 to 2013. Meanwhile the cardiovascular mortality in South Asia has increased by 97.5% during the same period.[1] This is a matter of grave concern as this increase will pose a great strain on the health budget of the countries in this region.

This increase is driven by population growth, an aging population, adverse lifestyle practices and inadequate control of cardiometabolic risk factors. These cardiometabolic risk factors include hypertension, diabetes mellitus and dyslipidemia. Not only has cardiovascular disease prevalence increased in South Asia but there has also been a marked rise in the incidence of diabetes mellitus in this region.[2] Diabetes mellitus is a significant risk factor for cardiovascular disease. The UKPDS study has confirmed the relationship between glycemic control and cardiovascular disease especially myocardial infarction.[3] The hyperglycemia and associated dyslipidemia in diabetes mellitus leads to atherosclerosis. Atherosclerosis per se does not have any symptoms but it can lead to sudden and severe life-threatening complications. Atherosclerosis is not a localized pathology. It involves all parts of the circulation causing coronary artery disease, peripheral vascular disease and stroke in the diabetic patients. Assessment of atherosclerosis by non-invasive methods is a useful investigatory modality. For this purpose ultrasonography measurement of Carotid intima-media thickness can be used as a useful substitute of angiography for assessment of atherosclerosis.[4] Different studies have shown the reliability of common carotid IMT as a predictor of generalized atherosclerosis especially in cases of ischemic stroke and cardiovascular death.[5] It can predict the occurrence of future ischemic heart disease and ischemic stroke in susceptible patients and thus identify the population at risk.[6] CIMT can also be used to identify the presence of atherosclerosis; its progression and also response to treatment.[7] Carotid Doppler studies are a practical and convenient method to identify the presence clinical and preclinical atherosclerosis in diabetic patients. CIMT has been said to show association with coronary artery narrowing without overt history of coronary heart disease.[8] This modality will also help recognize the effectiveness of preventive strategies adopted to manage the atherosclerosis. CIMT is a useful tool in the risk stratification of patients with cardiovascular risk factors. Thus another role of CIMT is risk prediction for cardiovascular events as it shows relatable risk estimation when compared with cardiovascular risk predictors like Framingham score. The combined risk estimation using both the modalities may have synergistic effect on the predictive value of these methods.[9]

The risk factors associated with atherosclerosis are modifiable and non- modifiable. Among the modifiable risk factors obesity, physical activity, lifestyle, hypertension, diabetes mellitus, and dyslipidemia all have been found to be associated with increased CIMT. The association of diabetes mellitus with CIMT has shown variable results. Thus this association needs to be verified to better predict the development of atherosclerosis especially in diabetic patients.

The objective of our study was to ascertain the association of carotid atherosclerosis, determined by carotid intimo-medial thickness and presence of carotid plaque, with type 2 diabetes mellitus and to determine the association of glycemic control with carotid intimal medial thickness and presence of carotid plaque in these subjects.

MATERIALS AND METHODS

This study was a cross-sectional comparative study. It was conducted at the Medical and Radiology Departments of Creek General Hospital, United Medical and Dental College; Karachi from June 2015-May 2016. The cases were adult patients of both genders with type 2 diabetes mellitus presenting to the Medical Out-Patient Department and controls were age and gender matched non-diabetic subjects. Patients were diagnosed to have diabetes mellitus according to OGTT criteria, HbA1c levels, or known to have diabetes mellitus and taking hypoglycemic drugs. Patients were diagnosed to have type 2 diabetes mellitus when they were diagnosed with the disease when the subject was above 35 years old irrespective of type of hypoglycemic therapy or were being treated with diet control and oral hypoglycemic drugs irrespective of age at diagnosis. Patients with acute illnesses, history of overt coronary heart disease, congestive cardiac failure, stroke, chronic kidney disease, thyroid disease, liver

disease, rheumatologic disease, thyroid disease and pregnancy and were excluded from the study. Further comparison of the diabetic subjects with satisfactory glycemic control (HbA1c≤7.0) and diabetic subjects with unsatisfactory glycemic control (HbA1c>7.0) was done.

Informed consent was obtained from all participants. The study was approved by the ethical review committee of the institution.

Detailed history and physical examination was recorded on a structured proforma. The factors included age, gender, weight, height, BMI, duration of diabetes, blood pressure and smoking. Fasting and random blood glucose was recorded for all patients. Glycemic control assessment was through measurement of HbA1c levels. Hemoglobin A1c was measured by automated high-performance liquid chromatography analyzer (Bio_RadDiamat, Milan, Italy); The upper limit of normal for our laboratory was 5.8%.

All patients who were included in the study underwent B-mode carotid Doppler ultrasound to measure the carotid intima media thickness. All Doppler studies were performed by the same operator. The studies were performed using a linear probe (Toshiba Nemio 35) with a linear transducer of 7.5 MHz. The procedure was performed with the subject lying in the supine position and the head slightly tilted to the opposite side. The posterior walls of both the common carotid arteries, 1.5 cm proximal to the carotid bulb were measured. The distance between leading edge first bright line of far wall (lumen-intima interface) and the leading edge of the second bright line (media-adventitia interface) was measured as carotid intima-media thickness. Frozen images of the segments for CIMT were calculated by the computer. Mean value of both arteries was taken as CIMT for analysis in the study. The common carotid artery was scanned transversely and longitudinally for presence and estimation of atheromatous plaques. For the purpose of the study a plaque was defined as an area where IMT was locally increased to more than 1.10 mm. The data was recorded for presence or absence of plaques.

The data was entered and analyzed on SPSS version 20.0. Mean and standard deviation was computed for quantitative variables like age, BMI, duration of diabetes, systolic and diastolic blood pressures, mean blood pressure, fasting and random blood sugar levels, HbA1c levels, total cholesterol, LDL cholesterol, HDL cholesterol and serum triglycerides levels, and CIMT. Frequency and percentages was computed for categorical variables like gender, presence or absence of diabetes mellitus, the presence or absence of optimal glycemic control among the diabetic patients, presence or absence of hypertension, presence or absence of dyslipidemia, presence or absence of carotid plaques.

Association of diabetes with CIMT was computed through Student's t test. P-value of <0.05 was considered significant. Association of glycemic control i.e satisfactory (HbA1c≤7) and unsatisfactory (HbA1c>7) with CIMT was assessed through Student's t-test. P-value of <0.05 was considered significant.

Association of presence of plaques within the cases and controls was computed through Chi-square test. P-value of <0.05 was considered significant. And association of carotid plaques with degree of glycemic control was measured through Chi-square test taking p-value of <0.05 as significant.

RESULTS

A total of 237 patients 105(44.3%) males and 132(55.5%) females were included in the study. There were 119(50.2%) cases and 118(49.8%) controls. The patients had a mean age ±SD of 51.9±14.8 years. This was 55.1±14 years in cases and 48.7±14.96 years in controls. The BMI (mean±SD) of the subjects was 25.8±5.8 kg/m^2. Other data calculated for the study population is shown in Table-I. The average duration of diabetes among the diabetic population was 6.9±5.2 years. As expected the glycemic indices were all higher in diabetic patients while they were within normal range in non-diabetic

controls. The fasting lipid profile indicated that all fractions of the lipid profile were higher in diabetic patients than in controls with the difference seen mainly in total cholesterol, LDL cholesterol and triglycerides. The study population had a mean CIMT of 0.91±0.17 mm being 1.0±0.18 mm in cases while in controls it was 0.83±0.12 mm. The cases and controls were analyzed for association between presence of diabetes and CIMT measurement showing a strong association with a p-value of <0.000 (Table-II). The presence of carotid plaque was also significantly associated with diabetes (p-value<0.001).

Variables		Total population	Patients with diabetes(cases) N=119(50.2%)	Patients without diabetes(controls) N=118(49.8%)
Age (years)		51.9±14.8	55.1±14.0	48.7±14.9
Gender-number(percent)	Male	105(44.3)	59(49.6)	46(39)
	Female	132(55.7)	60(50.4)	72(61)
HYPERTENSION number(percent)	Yes	122(51.5)	63(52.9)	59(50)
	No	115(48.5)	56(47.1)	59(50)
Duration of Diabetes (years)		3.47±5.0	6.9±5.2	Na
Weight (kg)		65.75±14.5	67.8±14.9	63.65±13.8
Height (cm)		157.5±15.5	156.5±20.9	158.4±6.5
BMI		25.8±5.8	26.4±6.6	25.2±4.8
Systolic BP (mmHg)		126.6±17	129.2±15.2	124±18.4
Diastolic BP (mmHg)		82.2±10.1	82.6±8.3	82±11.8
Fasting Blood Glucose (mg/dl)		113.3±55.2	151.2±54.7	75±14.1
Random Blood Glucose (mg/dl)		185.9±102.0	261.9±92.5	109.2±23.8
HbA1c		6.98±2.5	8.8±2.3	5.1±0.5
Total Cholesterol (mg/dl)		178.9±36.1	191.0±32.4	166.6±35.6
LDL (mg/dl)		114.8±36.1	122.0±26.0	107.5±28.4
HDL (mg/dl)		39.5±10.0	39.6±10.6	39.4±9.4
Triglyceride (mg/dl)		173.7±87.68	215.8±99.1	131.3±44.5

Table-I. Characteristics of study population

Variable		Subjects with Diabetes Mellitus	Subjects Without Diabetes Mellitus	P-Value
Carotid Intimomedial Thickness		1.0±0.18	0.83±0.12	0.000*
Carotid Plaque	Yes	22(18.5)	6(5.1)	.002**
	No	97(81.5)	112(94.9)	

Table-II. Comparison of CIMT and carotid plaque among the diabetic and non-diabetic population
*Student t-test **Chi-square test

The comparison of diabetic subjects with satisfactory glycemic control, which was taken as HbA1c level≤7.0, and un-satisfactory glycemic control is shown in Table-III. There was marked difference in the glycemic indices i.e fasting blood glucose, random blood glucose and HbA1c, in the triglyceride fraction of the lipid profile as well as both systolic and diastolic blood pressure among the two groups. But more notable is the fact that there was no association of the level of glycemic control with CIMT measurement or the presence of carotid plaque. (Table-II)

Variable		Satisfactory Glycemic Control	Unsatisfactory Glycemic Control	P-Value
Carotid Intimomedial Thickness (mm)		1.0±0.20	0.98±0.20	0.13*
Carotid Plaque	Yes	12(36.4%)	28(32.6)	0.42**
	No	21(63.6)	58(67.4)	

Table-III. Comparison of CIMT and carotid plaque among the diabetic population with satisfactory and unsatisfactory glycemic control
*Student t-test **Chi-square test

DISCUSSION

The study has shown significant association of CIMT with type 2 diabetes mellitus as compared to normal controls. Carotid Doppler is an important investigation modality to ascertain atherosclerosis. It is has been used extensively as a research tool for evaluating the effect of cardiovascular risk factors on the circulation. Asymptomatic atherosclerotic involvement of the cerebral, coronary and peripheral vasculature can be effectively assessed by measuring the CIMT through Doppler studies.

It was observed in an Indian study that CIMT of the diabetic patient was significantly higher than non-diabetic patient.[10] Another local study showed that eighty percent of patients with type 2 diabetes mellitus had a high CIMT while the subjects without diabetes showed a 20% prevalence of high CIMT. Our study has shown a significantly high CIMT in diabetic subjects (1.0±0.18 mm) while this was 0.83±0.12 mm in non-diabetic subjects while the CIMT in the whole study population was 0.916±0.17 mm which is comparable to CIMT seen in some Indian studies.[11,12] These studies investigated CIMT in diabetic patients with ischemic stroke and with coronary artery disease respectively. A local study revealed that a CIMT more than 0.8mm increased the risk of ischemic stroke in diabetic patients and recommended its use as a screening tool for such patients.[11] In most studies a CIMT of a healthy middle-aged adult has been taken to be 0.6-0.7 mm and CIMT of more than 1.00mm is abnormal.[13] CIMT is related to age, increasing at around 0.005-00.010mm each year.[14] Increased CIMT is observed in subjects with impaired glucose tolerance. The presence of carotid plaques was also seen to be significantly associated with type 2 diabetes mellitus. In our study 18.5% of diabetic patients had a plaque while only 5 % of non-diabetic subjects were observed to have a plaque. The presence of a carotid plaque is known to be associated with cerebrovascular accidents.[15] The presence of plaques was observed in about 83% of diabetic patients with ischemic strokes while 16.7% of diabetic patients without ischemic stroke had carotid plaques.[11] This percentage is quite similar to that seen in our study.

Type 2 diabetes mellitus places patients at an increased risk for coronary artery disease and cerebrovascular disease. This increased risk is also seen in patients with impaired glucose tolerance and well-controlled type 2 diabetes mellitus with early diagnosis. It has been observed that there was a significant relationship of glucose levels after a glucose challenge test with CIMT in these patients.[16]

Studies have shown association of age, duration of diabetes, high non-HDL cholesterol, being a smoker and increased systolic blood pressure with an increased value of CIMT in patients with type 2 diabetes mellitus.[17] An Asian study also reveals association of age, duration of diabetes, both systolic and diastolic blood pressures and HDL levels with carotid intima-media thickness in patients with type 2 diabetes mellitus.[18] Glycemic control as represented by HbA1c in type 1 diabetes patients showed a significant relationship with CIMT only in female patients and not in male patients.[19]

Our study did not show any association of glycemic control with CIMT. This finding is supported by epidemiological evidence which reveals that tight glycemic control did not show a significant reduction in adverse cardiovascular events. It is therefore the presence of this atherogenic risk factor and the duration of their presence that is responsible for the presence of atherosclerosis. It may be that chronic hyperglycemia leads to atherosclerosis not the status of current hyperglycemia which leads to atherosclerosis. Multiple mechanisms are responsible for atherosclerosis and increased cardiovascular risk seen in patients with type 2 diabetes mellitus. Hyperglycemia, dyslipidemia, adiposity, hypertension and the pro-inflammatory effects of diabetes all play a role in development of atherosclerosis. In a Middle-Eastern study subjects with type 2 diabetes who had features of metabolic syndrome excluding the blood pressure component had a significantly higher

mean CIMT compared to subjects without the metabolic syndrome.[20] Thus it is not only the hyperglycemia which leads to atherosclerosis but other proatherogenic factors which are a component of the diabetes syndrome. Other studies have shown the association of metabolic syndrome with a greater CIMT.[21,22] A study reveals that hypertension is most significantly associated with high CIMT in metabolic syndrome.[23] It is also interesting to note that CIMT is higher in relatives of subjects with type 2 diabetes mellitus.[24] This may be because of other metabolic abnormalities that develop before the manifestation of overt hyperglycemia.

Formation of atherosclerotic plaque is a feature of advanced atherosclerosis. The presence and duration of atherogenic risk factors is responsible for formation of plaques. Although carotid plaque presence showed a significant association with type 2 diabetes mellitus but no association was seen with glycemic control among the diabetic cohort in our study.

Our study reveals that the development of atherosclerosis is intimately associated with type 2 diabetes mellitus because of aggregation of multiple risk factors in this syndrome. The role, contribution and relationship of other atherogenic factors in type 2 diabetes, which lead to atherosclerosis, needs to be investigated.

CONCLUSION

This study confirms the observations that carotid thickness as measured by CIMT on Doppler ultrasonography is significantly increased in diabetic patients and there is no association between satisfactory and unsatisfactory glycemic control and CIMT among the diabetic subjects. The same results are seen with the presence of carotid plaque and type 2 diabetes mellitus.

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PREVIOUS RELATED STUDY

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AUTHORSHIP AND CONTRIBUTION DECLARATION

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2	Dr. Farzana Rehman	Research, Write-up and collection of data	
3	Dr. Samina Ghaznavi	Research and writing	
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