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Research Paper

A Comparative Study of the Carotid Intima Medial Thickness Between Diabetic and Non Diabetic Patients

Medical Science

KEYWORDS : DM – Diabetes Mellitus BMI - Body Mass Index CCA – Common Carotid Artery ICA – Internal Carotid Artery CIMT – Carotid Intima Medial

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ABSTRACT

BACKGROUND AND OBJECTIVES:

Diabetes mellitus is a group of metabolic disorders and is worldwide in distribution. It has become a potential epidemic and is reported to be the seventh leading cause of morbidity and mortality. Diabetic patients have a high preponderance to multiple vascular complications,which worsen with the duration and severity of diabetes, and thereby leading to death. The carotid intima medial thickening is a direct measurement of atherosclerosis and by evaluating it through B-mode ultrasound we will be able detect early phases of atherosclerosis. Through this study we aim to compare the carotid intima medial thickness between diabetic and non-diabetic population and also assess the relation between carotid intimal medial thickness in relation to microvascular morbidity in diabetic population. METHODS:This study was conducted at Mahatma Gandhi Medical College and Research Institute, Puducherry. It is a comparative analytical study conducted over a period of one and half years, involving two groups, each consisting of fifty patients. The study group constituted of diabetic patients and the control group constituted of age and sex matched non-diabetic patients who attended our hospital. Patients with impaired fasting glucose or impaired glucose tolerance, smokers, patients with history of using oral contraceptive pills were not included in this study. Subjects were assessed for carotid intimal medial thickness by measuring the intimal medial thickness of common carotid artery (CCA) on both right and left side by using 2D ultrasound. The presence or absence of plaques was also studied. RESULTS:From this study we were able to establish that CIMT is higher in diabetic patients in comparison to non-diabetic patients (p value 0.0001). We were also able to demonstrate a positive correlation between CIMT and microvascular complications. Retinopathy was found to occur more in diabetic patients in comparison to the non-diabetics. Similar correlation could be made for coronary artery disease ,cerebrovascular disease . CONCLUSION: We conclude that diabetes causes an increase in the CIMT and thereby predisposes patients to vascular complications. Therefore CIMT evaluation should be made routine in all diabetic subjects irrespective of duration of diabetes and its severity in order to prevent or slow down the process of atherosclerosis.

Introduction

Diabetes mellitus is a group of metabolic disorders characterized by the same phenotype of hyperglycemia. Defects in insulin secretion/action or both cause DM. DM causes long-term damage, dysfunction, and failure of many organs, especially the eyes, kidneys, nerves, heart, and blood vessels due to the chronic hyperglycemia. DM is worldwide in distribution and its prevalence has escalated in the last two decades. In 1985 it was estimated to be 30 million cases, which has risen to 382 million as in 2013. With the current rising trend of the prevalence of DM, the International Diabetes Federation believes that 592 million cases of DM will be established by the year 2035. Diabetes is a major cause of mortality. In 2010,diabetes was reported as the seventh leading cause of death in the U.S. A recent estimate in 2013 projected that diabetes was an underrated cause for almost 5.1 million deaths worldwide, which constitutes 8% of total deaths. In 2013,a worldwide estimate showed that 11% of healthcare expenditures was spent on diabetes patients. In India diabetes is a potential epidemic. It was estimated that in 2013 India had 65.1 million individuals with the disease, as when compared to 50.8 million in 2010. In 2000,India topped the world with the highest number of people with DM, having 30.7 million individuals with the disease, followed by China with 20.8 million and United States with 7.7 million.[1]

The major cause of morbidity and mortality in diabetic patients are the macro vascular complications such as coronary artery disease, cerebrovascular disease and peripheral vascular diseases and these account for the death of approximately 75-80% of the patients.[2-5]

Dyslipidemia frequently co-exists with type 2 DM, and thereby constitutes a vital role in the pathogenesis of expedited atherosclerosis. [6,7]

Atherosclerosis is generally asymptomatic unless severe. Therefore a direct study of the vessel wall is required to identify the affected persons in the early phase. The International atherosclerosis project states that the process of atherosclerosis eventuates in carotid, cerebral and coronary arteries almost simultaneously.[8] It was found that evaluation of the carotid intima-media thickness (CIMT) of the common carotid artery (CCA) by B-mode ultrasonography was a suitable method to inspect the arterial walls and detect the early stages of the atherosclerosis.[9-11]

Lorenz et al[12] states that CIMT is found to be an intermediate phenotype for early atherosclerosis. CIMT was found to be increased in type 2 diabetes individuals. This increase in carotid intima-media thickness attributes to an increase in risk of these patients in developing and accelerating the diabetes related complications such as coronary artery disease, cerebrovascular disease, peripheral vascular disease, retinopathy, neuropathy and nephropathy. [13]

A recent study by Anjana et al[14] in 2015, which is a10 year follow-up of the CURES study, showed that Asian Indians have one of the highest and rapidly increasing incidence rates of diabetes warranting public health interventions to detect and target modifiable risk factors to decelerate the diabetes epidemic in this population. It is alarming that the span of complications attributed to poorly controlled diabetes are observed at a relatively younger age within the country. Poor diabetic control found in the Indian diabetic population is responsible for the micro and macro vascular alterations that manifest with diabetes, and can predispose these patients to further worse complications such as diabetic myonecrosis and muscle infarction.

In India, the migration of people from rural to urban areas and the change in life-style due to the economic growth are escalat-

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ing the prevelance of diabetes .Yet there remains a paucity of studies analyzing the accurate status of the disease due of the geographical, socio-economic, and diverse nature of such a large country, demanding urgent research and intervention.[14]

AIMS AND OBJECTIVES

- To compare the carotid intimal medial thickness between diabetic and non-diabetic population.
- To assess the relation between carotid intimal medial thickness in relation to microvascular morbidity in diabetic population.

REVIEW OF LITERATURE

The major morbidity and morbidity of diabetes are due to the chronic complications which affects many organ systems. They can be vascular and non-vascular. The vascular diabetic complication maybe sub-grouped into micro vascular (neuropathy, retinopathy and nephropathy) and macro vascular (CAD, PVD and CVD) complications. Non- vascular complications include infections, gastro-paresis and skin changes. The risks associated with these complication increases with the duration of prolonged hyperglycemia. Many of the type 2 DM individuals presents with complications at diagnosis as there is a long asymptomatic period of hyperglycemia.

Chronic hyperglycemia is identified as the prelude for micro vascular complications in both type 1 and type 2 DM. Large randomized trials have demonstrated chronic hyperglycemia reduction delays micro vascular complications and other factors may also modulate or alters the development of complications. Those patients with long standing DM on tight glycemic control never develop these complication, whereas on the other hand genetic susceptibility to develop a particular complication even in those having a good glycemic control also exist.

CAD events and mortality are 2 to 4 times commoner in individuals with type 2 DM and also evidence in favour of chronic hyperglycemia causing macro vascular complications remains less conclusive. These events correlate well with HbA1c, fasting and postprandial blood glucose levels and other factors such as hypertension and dyslipidemia.

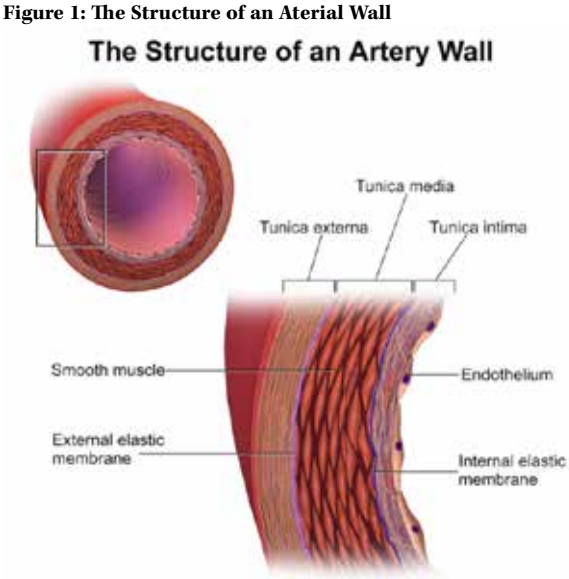
ATHEROSCLEROSIS:

Atherosclerosis, an inevitable association with ageing is believed to be a leading cause of human morbidity and mortality and is the forerunner of cerebrovascular and coronary artery disease and its development depends on a consortium of factors. In the middle-east and south Asian population there has been a sustained increase in atherothrombotic disorders and these have been contributed to lifestyle changes and dietary practices in addition to ageing. In type 2 diabetes mellitus patients, hypertriglyceridemia has proved to be consistently associated with increased risk for atherosclerosis. Enrichment of triglyceride rich particles with cholesteryl esters as a process of lipid exchange in populations with sustained increases in fasting or post prandial plasma triglyceride levels contributes to make these particles more atherogenic.[17]

Atherosclerosis is a slowly progressive disease, which pathologically involves the intima and media of medium and large sized arteries and leads to formation of lipid material and fibrous tissue containing lesions. In the early stage of atherosclerosis, the plaques and focal arterial wall thickenings usually do not impede on the arterial flow. Blood flow impairment results when the non-stenotic lesions are superimposed by thrombosis and thereby leading to end organ and tissue ischaemia.

The outer aspect of a normal artery is bounded by the internal elastic lamina and an endothelium lined intima in the inner aspect of the vessel. The external elastic lamina and an internal elastic lamina binds the media. The exterior of the vessel and the external elastic lamina bounds the adventitia.

Figure 1: The Structure of an Aterial Wall



EVALUATION OF CAROTID ARTERY INTIMA-MEDIA THICKNESS BY DOPPLER ULTRASOUND – AN INDICATION OF ATHEROSCLEROIS:[22]

Profound high rates of macro vascular disease morbidity and mortality is observed with patients with type 2 DM. Atherosclerosis is often asymptomatic unless severe and a direct examination of the vessel wall is often necessary to detect in the early stages the affected individuals. Atherosclerosis renders the vessels vulnerable to rupture and weakens the vessel walls and in turn also narrows and occludes the vascular lumen compromising on the major organ blood supply and there by causing stroke and myocardial infarction.

Significant lumen encroachment in atherosclerosis is only evident after tremendous mural changes had been experienced by the artery. So luminal encroachment measurement by angiography is an inadequate tool in the early atherosclerotic lesions. B-mode ultrasonography with its capability of measuring the intima medial thickness of the arterial wall proves to address these challenges. It proves to be an excellent tool to study the massive mural changes and early atherosclerosis. B- mode imaging measurement of extra-cranial intima media thickness correlates well with histo-pathological examination of specimens of human aortic and common carotid arteries.

3.11.1. Principles of B mode USG in measuring carotid:[23]

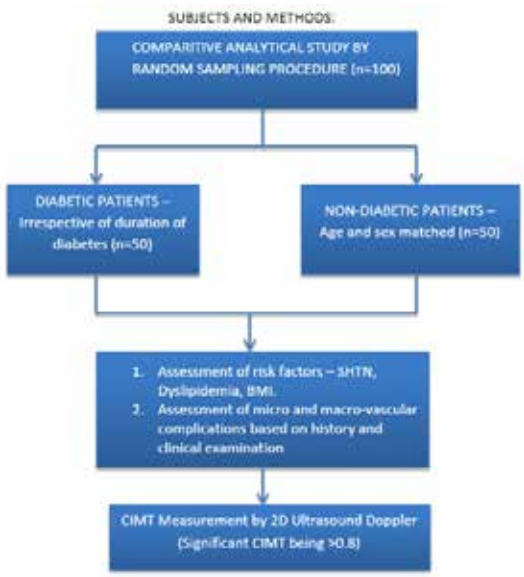
An electric linear transducer and a high resolution ultrasound B-mode colour Doppler imaging is usually used to perform ultra-sonographic scanning of carotid arteries. The anterior wall, lumen and the posterior wall are identified in two dimensional image of the carotid artery where both walls represent as echogenic and echo poor zones respectively.

The upper demarcation line of the echogenic zone (leading edge represent to the anatomic transition zone, which gives rise to an echo and the lower demarcation line of the echogenic zone (far edge) is defined by gain setting of records system and does not represent the anatomical boundary.

Therefore the "Leading edge principle" is used to assess the IMT using the upper demarcation of echogenic zone. The lead-

ing edge of the first echogenic zone is given by the interphase between blood and intima in the posterior wall. The media is shown by the leading edge of the second echogenic zone. The lumina-intima interface is represented by the first line and the collagen containing upper layer of adventitia is represented by the second line. Three determinations of IMT are conducted at the site of greatest thickness at each longitudinal projections and the site of greatest thickness is formed at two points, one cm upstream and one cm downstream. Then these values are averaged. As evaluated by B-mode ultrasound imaging, the normal intima medial thickness of the common carotid artery was 0.74+0.14 mm.65 Because of their superficial location, size and limited movement carotid arteries are the most suited for the study. So as a valuable marker for atherosclerosis ultrasound B mode measurement of carotid artery IMT can be used.[24]

Figure 2



OBSERVATION AND RESULTS:

Table 1: Descriptive Statistics for Demographic,Biochemical and CIMT parameters distribution between the 2 groups (Independent T test)

PARAMETERS	DIABETES	NON-DIABETES	p VALUE
MEAN AGE(yrs)	56.0	55.96	O.984
MEAN BMI(kg/m^2)	24.19	24.78	0.554
MEAN SBP(mmhg)	125.76	125.08	0.757
MEAN DBP(mmhg)	78.96	82.36	0.005
MEAN HbA1C%	7.724	6.464	0.0001
VASCULAR COMPLICATIONS%	74	12	0.0001
CIMT%	60	4	0.0001
PLAQUE%	62	6	0.0001

Table 2 Comparison of CIMT with each vascular complication

Parameters	Retinopathy (n=22)	CAD (n=19)	Neuropathy (n=11)	CVD (n=9)	Nephropathy (n=7)
CIMT>0.8	86.4%	94.7%	63.6%	100%	85.7%
P value	0.0001	0.0001	1.000	0.0007	0.219

FIGURE 3 Distribution of CIMT among subjects having vascular complications

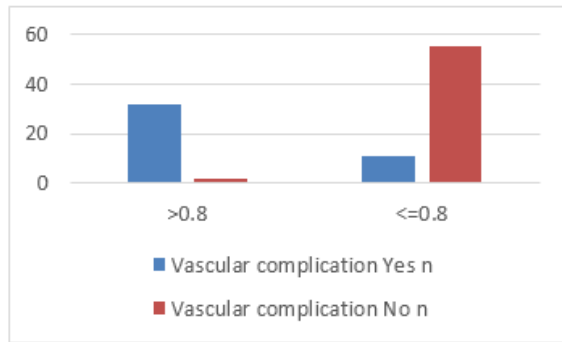


Figure 3 shows distribution of CIMT among subjects having vascular complications. Out of the 43 patients having vascular complications, 32 patients had CIMT >0.8 (74.4%) , 11 patients had CIMT <=0.8 (25.6%). Out of the 57 patients who had no vascular complications, 2 patients had CIMT >0.8 (3.5%), and 55 patients has CIMT <= 0.8 (96.5%). On comparing between those patients who had vascular complications and those who did not for the presence of significant CIMT >0.8, there is a statistically significant difference in those having vascular complications (p value 0.0001).

DISCUSSION:

- The values of intima medial thickness on both sides were obtained. The mean value was calculated and values greater than 0.8 mm were considered to be abnormal.
- This study was conducted in MGMCRI from January 2014 to May2015. In our study the mean duration of diabetes was 7.54 years. 43% of the patients had vascular complications, out of which 74% belonged to the diabetic group. (p value 0.0001).
- Among 74% diabetics with vascular complications, 44% had retinopathy, 34% had CAD, 18% had CVD, 22% had neuropathy and 14% had nephropathy and 2% had PVD.
- From this study a strong linear-association can be established between the duration of diabetes and the carotid intima media thickness (p value 0.001)
- CIMT was positively correlated to the presence of CAD, CVD and retinopathy, p values being 0.0001,0.007,0.001 respectively.
- Therefore the identification of abnormal CIMT in diabetics predicts the risk of vascular complications.
- Patients with greater CIMT had higher incidence of plaques (p value 0.0001).
- From this study we were able to establish that CIMT is higher in diabetic patients in comparison to non-diabetic patients.
- We were able to demonstrate a positive correlation between diabetes and vascular complications, in comparison to the non-diabetics. Retinopathy was the most commonly occurring complication as observed in our study, following which occurred neuropathy, then cardiovascular disease and cerebrovascular diseases. Peripheral vascular disease was seen only in one patient.

AGE AND SEX DISTRIBUTION:

- In our study, the mean age of diabetic population was 56.0 years, as compared to non-diabetics, which was 55.96 years.
- In the study by Agarwal et al[15], the mean age for the study group was 59.78 years.
- In the study by Gomez-Marcos et al[27], the mean age distribution was 60.23 years.
- Cases and controls were well matched with respect to age

and sex among diabetics and non-diabetics in our study. There was no statistically significant difference in the distribution of age and sex between the two groups in our study, p value being 0.984 for age and 0.420 for sex distribution.

DURATION OF DIABETES MELLITUS:

- In our study, the mean duration of diabetes was 7.54 years.
- In the study by J Ahmad et al[23], the mean duration of diabetes was 7 years.
- The duration of diabetes had a steady linear correlation with the duration of diabetes (p value 0.012).

SYSTEMIC HYPERTENSION:

- Systemic hypertension was the most common co-existing and co-morbid illness found in the diabetic population. It was present in 24% of the diabetics and 32% of the non-diabetics in our study. There was no statistically significant difference between the two groups in our study with respect to hypertension (p value 0.373)
- The mean SBP for diabetic population was 125.76mm Hg, and the DBP was 78.96mm Hg. There was no statistically significant difference between the two groups with respect to the SBP, whereas there was such a difference with respect to DBP. The diabetic population had a significantly lower mean DBP than the non-diabetic (p value 0.005). In the study by Agarwal et al[15], the mean SBP was 140 mm Hg, and the DBP was 86.67mm Hg.
- In the study by Gomez-Marcos et al[27] the mean SBP was 136.22 in the diabetics and the mean DBP was 83.58 for the same population.

BODY MASS INDEX:

- In our study the mean BMI was 24.19 among diabetic group. On comparing the two groups there was no statistically significant difference (p value 0.554).
- In the study by Agarwal et al[15], the mean BMI was 26.40.
- In the study by Gomez-Marcos et al[27] the mean BMI was 29.77.

GLYCOSYLATED HAEMOGLOBIN (HbA1C):

- In our study, the mean HbA_1C was 7.724 % among diabetic group.
- In the study by Agarwal et al[15], the mean HbA_1C was 7.64%.
- In the study by J Ahmad et al[23], the mean HbA1C was 8.63 among the diabetics.
- As we have done in this study, in a recent study, the ADVANCE trial (Action in Diabetes and Vascular disease: Preterax and Diamicron-MR Controlled Evaluation)[76] too HbA1C value was considered as the parameter to express the severity of diabetes. Fox et al[14] have demonstrated in their study that HbA1C provides a global index of glycemic exposure and is a robust predictor of complications than fasting blood glucose. Likewise we have included HbA1C as our diagnostic parameter due to less biological variability and standardaized laboratory methods.

SERUM LIPID PROFILE:

- In our study, the mean total cholesterol was 196.24mg%, triglycerides was 135.82 mg% , HDL was 37.44 mg%, LDL was 103.54mg% among diabetic group.
- In the study by Agarwal et al[15] – the mean Total cholesterol of 182.08 mg %, triglyceride was 155mg %, HDL was 42.46 mg%, LDL was 110. mg% among diabetic group

CAROTID INTIMA MEDIA THICKNESS:

- In our study, the mean CIMT was 1.0302 among diabetics as compared to 0.6754 of the non-diabetic group, which was statistically significant (p value 0.0001).
- In the study by Mohan et al[21] on intima-medial thickness of carotid artery in the south Indian diabetic and non-diabetic population, it has been demonstrated that the mean intimal-media thickness of the diabetic subjects was 0.95 mm were significantly increased than those of the non-diabetic subjects with 0.74mm, showing p value 0.001. In the study by Agarwal et al[15], the mean CIMT among diabetic group was 0.840.
- CIMT AND ITS ASSOCIATION WITH VASCULAR COMPLICATIONS:
- In our study, 43% of patients had vascular complications, out of which 74% belonged to the diabetic group. The result was statistically significant (p value 0.0001). Among 74% diabetics with vascular complications, 44% had retinopathy, 34% had CAD, 18% had CVD, 22% had neuropathy and 14% had nephropathy and 2% had PVD.
- In the study by Snichi Teno et al[7] 31.6% of the diabetic patients had retinopathy, 11.6% of them had nephropathy.
- In the study by Kota et al[28], 16% of the diabetics had CVD.
- In our study, 60% of the diabetic patients had a significantly high CIMT(p value 0.0001)
- In the study by Shwertz et al[30] 63% of diabetic patients with CAD had increased CIMT.
- In the study by Rema et al[25] 19.6% of the diabetic patients with increased CIMT had retinopathy.
- There is no statistically significant relation between neuropathy and nephropathy with CIMT. But in the study by Kim et al[29] it was observed that neuropathy had a positive correlation with CIMT.
- In this study at any age point carotid intima media thickness values of the diabetic patients (1.302mm) are significantly greater than that of the non diabetic patients (0.6754), irrespective of the co-morbid conditions (p value 0.0001)
- From this study a strong linear-association can be established between the duration of diabetes and the carotid intima media thickness (p value 0.001)
- CIMT was positively correlated to the presence of CAD, CVD and retinopathy, p values being 0.0001,0.007,0.001 respectively.
- Therefore the identification of abnormal CIMT in diabetics predicts the risk of vascular complications.
- Patients with greater CIMT had higher incidence of plaques (p value 0.0001). Therefore diabetic patients with abnormal CIMT have increased liability to develop carotid plaques and thereby have an increased risk to develop CAD and CVD.
- Systemic hypertension was found to be the most common co-morbid illness among diabetic patients.
- The diastolic blood pressure value of diabetics was found to be significantly lesser when compared to the non-diabetics (p value 0.005).
- Abnormality in serum lipid levels were found in diabetics in the form of elevated total cholesterol (p value 0.061), triglycerides (p value 0.0001), LDL (p value 0.040). Though hirayama et al[31] had said in their study that HDL concenteration is a predictor of carotid atherosclerosis in DM , there was no positive association between HDL values being compared between the two groups (p value 0.215) in our study.
- The HbA1C values were higher in the diabetic patients in comparison to the non-diabetics (p value 0.0001)
- There was no statistically significant correlation between the two groups with respect to BMI.
- Similarly there were no statistical differences occurring in the distribution of the demographic parameters (eg: Age, Sex)

THE POSSIBLE LIMITATIONS OF THIS STUDY:

1. The type of diabetes was not considered.
2. Impaired fasting glycemia and Impaired glucose tolerance

were not included in this study.

3. Smoking and Hypothyroidism are independent risk factors for increasing CIMT. But we have not included these factors in our study.

CONCLUSION

From this study we were able to establish that CIMT is higher in diabetic patients in comparison to non-diabetic patients. We were able to demonstrate a positive correlation between diabetes and vascular complications, in comparison to the non-diabetics. Retinopathy was the most commonly occurring complication as observed in our study, following which occurred neuropathy, then cardiovascular disease and cerebrovascular diseases. Peripheral vascular disease was seen only in one patient. A positive correlation could be established between CIMT and the vascular complications. Patients with retinopathy had the most association with increased CIMT, second most positive correlation was for coronary artery disease, and then cerebrovascular disease. It was observed that fasting triglyceride and LDL cholesterol was increased in diabetic subjects in comparison to the non-diabetic. Higher incidence of plaque was observed in diabetic. We conclude that CIMT measurement is a surrogate marker of vascular complications and ultrasound screening of carotid intima medial thickness of diabetic patients should be made mandatory to identify early atherosclerosis and thereby prevent the development or further acceleration of both micro and macro vascular complications by prompt initiation of preventive or therapeutic interventions

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