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Research Article

Carotid Intima Media Thickness in Diabetic and Non Diabetic Subjects: A Study from Rural Hospital

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Abstract: Atherosclerosis typically occurs over a period of many years, usually many decades. After a generally prolonged "silent" period, atherosclerosis may become clinically manifest. Evaluation of intima media thickness is considered as surrogate marker of Atherosclerosis. B mode ultrasound was found to be a suitable non invasive method to visualize the arterial walls and to monitor the early stages of the atherosclerotic process. Purpose of this study was to find out carotid intima media thickness in patients with diabetic and non diabetic patients and its correlation with associated risk factors like age, sex, hypertension, and smoking. A total of 100 patients were selected with 50 patients each in diabetic and non diabetic groups. Study protocol included detailed clinical history, clinical examination and investigations. Patients were subjected for carotid doppler examination and other relevant investigations pertaining to their clinical status. The mean intima media thickness values of the diabetic subjects (0.12mm) were significantly higher than those of the non-diabetic subjects (0.07 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. Intima media thickness showed a correlation with age, gender, hypertension, HbA1C, duration of diabetes with significant p value. Diabetic subjects have higher intima media thickness values than non-diabetic subjects. Diabetes, duration of diabetes, age, gender and hypertension are the most important risk factors associated with increased intima media thickness. By using non invasive ultrasound guided measurement of carotid intima media thickness it is possible to detect atherosclerosis in risk groups at the earliest during asymptomatic period and to prevent related complications.
Keywords: Atherosclerosis, Carotid intima media thickness, Diabetes mellitus, Dyslipidemia, Hypertension

INTRODUCTION

Sonographic evaluation of the carotid artery intima media thickness is a simple, non-invasive and reproducible imaging parameter to evaluate atherosclerosis and atherosclerotic vascular diseases. Recently, considerable attention has been directed at the wall thickness of the carotid arteries as an early marker of atherosclerotic disease and as a means of showing the effectiveness of medical therapies in treating atherosclerosis. Non invasive techniques such as B-mode ultrasound can directly assess the intima–media thickness (IMT), which corresponds to the thickness of the histologic intima and media [1, 2, 3]. Ultrasound imaging of carotid vessels can provide information on Carotid Intima Medial Thickness (CIMT), 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 and cerebrovascular events. Such non-invasive screening procedures are valuable in identifying diabetic patients at risk for coronary artery disease and cerebrovascular disease. In clinical settings, this can potentially lead to early interventions. The carotid arteries are among the vessels that are prone to developing overt atherosclerotic lesions in the presence of risk factors such a cigarette smoking, Hypertension (HTN), diabetes mellitus (DM) and dyslipidemia [4, 5]. Patients with diabetes mellitus suffer unduly from premature and severe atherosclerosis. The Framingham study pointed out that diabetic individuals have higher serum concentrations of lipids and more hypertension, obesity, and thus are more prone to metabolic syndrome and it's squeals, namely coronary artery disease (CAD), cerebrovascular disease and vascular atherosclerosis[6]. In type 2 DM, carotid intimal thickness is significantly higher than in corresponding healthy age and sex matched non diabetic subjects. There is also evidence for an excess prevalence of intimal thickening and

atherosclerotic lesions in patients suffering from definite hypertension compared with normotensive controls [7,8,9]. Hence measurement of carotid intimal thickness using high resolution B mode ultra sonography which is non invasive well validated method is used to assess early manifestations of atherosclerosis such as early cardiovascular disease, transient ischemic attack, stroke in asymptomatic as well as high risk patients such as dyslipidemia, DM, HTN and cigarette smoking.

MATERIAL AND METHODS

This is a cross sectional hospital based study. A total of 100 patients were selected with 50 patients each in diabetic and non diabetic groups. After taking consent, patients were subjected for carotid Doppler examination and other relevant investigations pertaining to their clinical status. Ethics committee approval was taken for the study.

Inclusion Criteria

- Patients aged more than 30 years with type2 diabetes mellitus

Exclusion Criteria

- Patients with ischaemic heart disease (acute coronary syndrome, stable angina, prior history of coronary artery bypass graft, per cutaneous coronary angioplasty)
- Patients with congestive heart failure
- Patients with renal disease both acute and chronic
- Patients with stroke
- Patients with type 1 DM

Definition of terms

Patients on oral hypoglycaemic drugs, Insulin or those having fasting blood sugar > 126 g/dl were regarded as having diabetes mellitus. Those with blood pressure > 140 / 90 mm Hg taken twice or those on antihypertensive drugs were defined as hypertensive. A diagnosis of hyperlipedemia was made if total Cholesterol is > 200 mg/dl, Triglycerides > 150 mg/dl, and LDL > 100 mg/dl. Height, waist and hip circumference were measured in centimetres by using a non-stretchable standard tape with a metal buckle at one end over the light clothing. Waist circumference was measured in the centre of the iliac crest and the coastal margin, and hip circumference was measured at the widest point on buttocks below the iliac crest. . Patients were divided in to non-obese and obese on the basis of body mass index (BMI). A BMI of 27.3 Kg/m**2** or more in subjects indicates obesity. BMI=Body weight (Kg), Height^2 (meters).

Current smokers were defined as those who smoked any form of tobacco in the previous 6 months while former smoker were those who had quit more than 6 months earlier.

Statistical Analysis

Data are presented as means for continuous data and as n (%) for frequency data. A P value of < 0.05 was considered to indicate statistical significance.

RESULTS

Age distribution

In our study maximum number of subjects belonged to sixth decade (Table 1). In age group 40-50 years, CIMT in cases is 0.08±0.03, in controls, it is 0.07±0.01. In age group 51-60 years, CIMT in cases is 0.11±0.04, in controls, it is 0.074±0.01.In age group 61-70 years, CIMT in cases is 0.13±0.021, in controls, it is 0.07±0.02 (Table 2).

Mean CIMT (0.13±0.021) is more in age group 61-70 years, as age increases, CIMT also increased in cases.

Table 1: Age distribution

Age in years	Cases		Controls	
	No	%	No	%
40-50	10	20	11	22
51-60	13	26	12	24
61-70	27	54	27	54
Total	50	100	50	100

Table 2: Comparison of CIMT in Two Groups Studied According To Age in Years

Age in years	Cases	Controls	P value
40-50	0.08±0.03	0.07±0.01	0.151
51-60	0.11±0.04	0.074±0.01	0.014
61-70	0.13±0.021	0.07±0.02	0.105

Gender distribution

In this study there are 37(74%) males and 13(26%) females in both cases and control groups (Table 3). In cases, Mean CIMT in males is 0.097±0.04 and in female's 0.17±0.030.In controls, Mean CIMT in males is 0.07±0.02 and in female's 0.07±0.024 (Table 4). In cases, females had increased CIMT than males as in our study.

Table 3: Gender distribution of patients studied

Gender	Cases		Controls	
	No	%	No	%
Male	37	74	37	74
Female	13	26	13	26
Total	50	100	50	100

Table 4: Comparison of CIMT in Two Groups Studied According To Gender

Age in years	Cases	Controls	P value
Male	0.097±0.04	0.070±0.02	<0.001
Female	0.17±0.030	0.07±0.024	0.217

Average CIMT

Out of 50 cases, 46 patients had CIMT between 0.06 – 0.20 cm (92%) and Out of 50 controls, 45 had CIMT between 0.06 – 0.20 cm (90%). Mean CIMT in cases is 0.121± 0.015 cm and in controls, it is 0.07 ±0.02 cm. Mean CIMT is significantly more in cases when compared to controls with p=0.035(Table 5).

Table 5: Comparison of Average CIMT In Two Groups Studied

CIMT	Cases		Controls	
	No	%	No	%
0.01-0.05	4	8	5	10
0.06-0.10	28	56	42	84
0.11-0.15	14	28	23	6
0.16-0.20	4	8	0	0
Total	50	100	50	100
Mean± SD	0.121±0.015		0.07±0.02	

Blood sugar levels

In this study 41(82%) cases FBS values were more than 140mg/dl and 50(100%)cases PPBS values were more than 200mg/dl(table 6 A). The effect of FBS and PPBS on CIMT among risk and non risk group was not significant (P =0.698)(Table 6B).

Table 6 A: Distribution of Sugar Parameters In Two Groups Of Patients Studied

Blood sugar parameters	Cases (n=50)		Controls(n=50)	
	No	%	No	%
FBS mg/dl				
<110	0	0	39	78
110-140	9	18	11	22
>140	41	82	0	0
PPBS mg/dl				
<140	0	0	24	48
140-200	0	0	26	52
>200	50	100	0	0

Table 6 B: Effect of FBS/PPBS on CIMT

NO	RISK	MEAN CIMT	NON RISK	MEAN CIMT
FBS	N=50	0.054±0.03	N=50	0.061±0.04
PPBS	N=50	0.054±0.03	N=50	0.061±0.04

Dyslipidemia

Patients with above the normal values in the profile were defined as risk group and patients with normal and below normal values were defined as non risk group**.** Normal Total Cholesterol value =<200 mg/dl, Triglycerides value=<150 mg/dl, High density lipoprotein (HDL) value=>40mg/dl, Low density lipoprotein (LDL) value=<100 mg/dl, Very low density lipoprotein (VLDL) value=<30 mg/dl (Table7A). The mean CIMT of the risk group is relatively higher than non risk group but p value was not significant (Table 7B).

Table7A: Distribution of Lipid Parameters in Two Groups Of Patients Studied

Lipid parameters	Cases (n=50)		Controls(n=50)	
	No	%	No	%
Total cholesterol mg/dl				
<200	18	36	39	78
>200	32	64	11	22
LDL mg/dl				
<130	27	54	40	80
>130	23	46	10	20
Triglycerides mg/dl				
<150	1	2	27	54
>150	49	98	23	46
HDL mg/dl				
<40	34	64	13	26
>40	16	32	37	74

Table 7 B: Effect of Lipid Profile on CIMT

	RISKGROUP		NONRISK GROUP			
Parameter	Mean CIMT	SD	Mean CIMTS	SD	Mean difference	P value
TC	1.2229	0.3647	1.1389	0.04485	0.0840	0.59(NS)
TG	1.2433	0.3412	1.1926	0.3958	0.0507	0.83 (NS)
HDL	1.2592	0.4069	1.1567	0.3771	0.1025	0.48 (NS)
LDL	1.2110	0.3819	1.1910	0.3973	0.0200	0.89 (NS)

DURATION OF DIABETES

Mean CIMT value 1.30±0.23 is highest between 7-10 years duration. There is incremental increase in CIMT value as the duration of DM progress (Table 8). Statistical significance was achieved when duration of DM was compared with CIMT value (P<0.001).

Table 8: Effect of Duration of Diabetes on CIMT

Duration Of Diabetes Mellitus	NO	MEAN CIMT
1-3 YEARS	20	0.77+ 0.19
4-6 YEARS	15	0.88+ 0.13
7-10 YEARS	15	1.30+0.23

HBA1C

Mean CIMT is more in patients with HBA1C value more than 7 %(Table9). Statistical significance was achieved when HBA1C was compared with CIMT value (P= 0.0004).

Table 9: Effect of HBA1C on CIMT among DM

HBA1C	Number	MEAN CIMT
>7%	37	0.09+0.04
<7%	13	0.05+0.03

HYPERTESION

There were 15 and 14 patients in risk and non risk group with CIMT <0.08 and 5 and 16 patients among risk and non risk group with CIMT >0.08. P Value= 0.04 which is significant. In this study mean CIMT of hypertensive and non hypertensive patients in study group were 0.12±0.25 and 0.09±0.03.Mean CIMT of hypertensive and non hypertensive patients in control group were 0.08±0.02 and 0.06±0.01 (Table 10).

Table 10: Effect of Hypertesion on CIMT

	CIMT <0.08	CIMT >0.08	TOTAL
Risk group	15	5	20
Non Risk group	14	16	30
TOTAL	29	21	50

SMOKING

In this study there was no significant effect of smoking on CIMT value (P value=0.39).

Table 11: Effect of Smoking on CIMT

Group	CIMT<0.08	CIMT>0.08	TOTAL
RISK	20	12	32
NON RISK	9	9	18
TOTAL	29	21	50

Body Mass Index

The mean CIMT in BMI < 23kg/m^2 is 0.046 and in BMI >23kg/m^2 mean CIMT is 0.072. There was no significant effect of BMI on CIMT (P value =0.006)

Table 12: Effect of BMI on CIMT

BMI(kg/m^2)	MEAN CIMT
<23	0.046±0.03
>23	0.072±0.02

Risk Factors

The mean CIMT in study group is more in patients with DM+HTN+SMOKING (0.16±0.25) compared to other patients (Table 13A).The mean CIMT in control group is relatively more in patients with HTN+SMOKING (0.08±0.001) group compared to other group (Table 13B).The mean CIMT is increased in DM+HTN+SMOKING group (0.16±0.25) which indicates risk factors contributes in the development of atherosclerosis (Table 13C).

Table 13A: Comparison of CIMT in DM with or Without HTN and Smoking

Risk factors	Number	Mean CIMT
DM+ HTN	18	0.12±0.25
DM WITHOUT HTN	13	0.09±0.03
DM+HTN+SMOKING	12	0.16± 0.25

Table13B: Comparison of CIMT in Non Diabetic with or without HTN and Smoking

Risk factors	Number	Mean CIMT
NON DM+ HTN	16	0.08±0.02
NON DM WITHOUT HTN	17	0.06±0.01
NONDM+SMOKING	8	0.06± 0.01
NONDM+HTN+SMOKING	11	0.08± 0.01

Table 13C: Comparison of CIMT in both Diabetic and Non Diabetic With Risk Factors

Risk factors	Mean CIMT
DM+HTN	0.12±0.25
DM+SMOKING	0.08±0.04
DM+HTN+SMOKING	0.16±0.25
NON DM+HTN	0.08±0.02
NON DM+SMOKING	0.06±0.01
NON DM+HTN+SMOKING	0.08±0.01

DISCUSSION

High resolution B-mode ultrasound is a non-invasive technique widely used to assess atherosclerosis in superficial arteries. It allows the accurate measurement of the distance between blood–intima and media–adventitia interfaces of the carotid wall, which is defined as carotid intima-media thickness (IMT) [10].

Several authors have suggested that carotid IMT is a marker of atherosclerosis in other vascular beds.[11]Indeed; an increased carotid IMT has been associated with a number of atherosclerosis risk factors, with the prevalence and extent of coronary artery disease (CAD) and with the incidence of new coronary

and cerebral events.[11,12,13,14] In view of these relationships, carotid IMT has been proposed as a surrogate endpoint to be used in clinical trials as an alternative to coronary atherosclerosis.[15].

B-mode imaging offers other advantages over angiography as it is non invasive risk free and less expensive. It can also be used to assess progression or regression of atherosclerosis by multiple serial measurements. With all these advantages many investigators since mid 1980s have used B-mode ultrasonography as important tool to assess atherosclerosis in various clinical trials [16]. Atherosclerosis is an inevitable accompaniment of ageing and its rate of development depends on several factors. Well known risk factors for accelerated atherosclerosis include hypertension, smoking, dyslipidemia and hyperglycemia. As several practical life style and pharmacological interventions for attenuating atherosclerosis development are available, it is necessary to identify subjects who are at early risk of developing accelerated atherosclerosis. Measurement of intima-media thickness of extra cranial carotid arteries by B mode ultrasound imaging correlated with histopathological examination. The intima media thickness is at present the best-studied ultrasonographic marker for early atherosclerosis. A thickening of intima-media complex not only reflects local alterations but also corresponds to generalized atherosclerosis. The normal intimal + medial thickness of common carotid artery as evaluated by B mode ultrasound imaging was approximately 0.80mm.[17] Few authors have approximated the CIMT with the formula as (0.009× Age+ 0.116).[18]. In present study mean age being 60 years and as the age increases, mean CIMT in cases had increased compared to controls. Sahoo R *et al.;* Salonen R *et al.;* Howard G *et al.;* and Allan PL *et al.;* showed a positive correlation between age and CIMT. [4, 19, 20, 21,] Cellular, enzymatic, and molecular alterations in the arterial vessel wall associated with aging were possible mechanisms for increase in incidence of atherosclerosis with age [22]. Mean CIMT is significantly more in male cases when compared to male controls .The present study correlates with the study done by Sahoo R *et al.;* [4] Protection from atherosclerosis in younger women is due to endogenous estrogen [23]. In our study mean CIMT was significantly more in cases when compared to controls. This study is correlating with the study done by Sahoo R *et al.*; [4]Type-2 Diabetes Mellitus is known to be a predisposing factor of atherosclerosis [24, 25]. Studies have confirmed that diabetic patients have an IMT greater than non diabetic individuals. Increased IMT in diabetes is independent of the other established risk factors [26]. The major biochemical abnormality that is characteristic of diabetes, chronic hyperglycemia is hypothesized as a causative factor of increased IMT. This hypothesis is also supported by the finding of a dose response relationship among diabetics, with poorly controlled diabetics or diabetics of long duration having higher rates of cardiovascular complications [27, 28]. In our study mean CIMT was significantly more in hypertensive persons when compared to non hypertensive persons. Similar findings were found in O'Leary DH *et al.;* Agarwal AK *et al.;* studies [14, 29]. Hypertension is a risk factor for the development of atherosclerosis. The endothelium is a likely central focus for the effect of the disease.

The cardinal pathological features of atherosclerotic lesion development are the presence of monocyte/macrophage and T cells, their localization in large conduit or elastic arteries in areas of low shear stress, proliferation and migration to the intima of smooth muscle cells, the deposition of increased amounts of connective tissue, and neovascularisation. Hypertensive arteries are thickened and there may be increased smooth muscle cell mass and cell number and increased depositions of connective tissue [30]. In this study there was no significant difference in CIMT between smokers and non smokers. Due to less number of patients this study failed to achieve statistical significance on effect of smoking on CIMT. In addition to accelerating atherosclerotic progression, long term smoking may enhance oxidation of low density lipoprotein cholesterol. [31, 32]In this study various parameters of lipid profile have shown a positive correlation with CIMT in study group though a statistical difference could not be assumed between risk and non risk group due to the less sample size. Similar findings were observed in other studies [3, 4, 13]. Hyperlipedemia may itself initiate endothelial injury and also promote the formation of foam cells. Platelet aggregation at site of endothelial injury causes proliferation of smooth cells. This together with foam cells is incorporated into the atheromatous plaque [33, 34]. Role of FBS PPBS as an influencing factor on CIMT is doubtful, due to the selection of random samples. In this study failed to assume significant difference between risk and non risk group due to the selection of random value. In this study there is positive correlation between duration of DM with CIMT value. This study is correlating with the MohanV *et al.;* study [35]. In this study there is positive correlation between HbA1C level with CIMT on comparing risk and non risk group in DM subjects. Some studies did not show statistical significant positive correlation between HbA1C and CIMT. [36, 37]In this study there is positive correlation between BMI and CIMT. This study was correlating with Sutton Tyrrell K *et al.;* study, which showed strong positive correlation of BMI with CIMT [38]. Some studies did not show statistical significant positive correlation between BMI and CIMT [39, 40].

CONCLUSION

The present study showed increased values of CIMT in DM patients. Along with DM risk factors like age, HTN, BMI, duration of DM, HBA1C, have a correlation with CIMT either directly or indirectly

influencing the disease process itself and contributing for atherosclerosis. Ultrasound guided CIMT measurement is non invasive, reproducible method for detecting early arterial structural changes associated with various risk factor for atherosclerosis. Hence measurement of carotid intima media thickness by ultrasound Doppler is reliable and helps in early medical intervention to take care of risk factors and life style modification. More prospective case control studies with large number of subjects are needed on this topic.

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