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Original research article

The risk factors for increased Carotid Intima Media Thickness (CIMT) in type-2 diabetes mellitus

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Abstract

The basic pathology that relates complications of Diabetes with blood sugar levels is atherosclerosis. The basic mechanism that is responsible for atherosclerosis in Diabetics is non-enzymatic reaction between glucose and proteins or lipoproteins in arterial walls. This ultimately leads to the formation of form Advanced Glycosylation End products (AGEs). Once formed, AGE-protein adducts are stable and virtually irreversible. This single centre, prospective, observational study was carried out in Diabetes unit of tertiary care hospital in patients of type 2 Diabetes Mellitus (T2DM). After the approval of institutional ethics committee, Diabetic patients attending the Diabetology unit of a tertiary care centre were recruited into the study. Overall increased CIMT was similar in males and females (36% vs. 35%). Mean BMI was not significantly different in two groups (26.56 ± 2.25 vs. 25.80 ± 1.65, p=0.105) as was the waist: hip ratio (0.87 ± 0.05 vs. 0.85 ± 0.05, p=0.225) respectively. More number of smokers had increased CIMT (25% vs. 8%, p=0.462). Systolic (138.08 ± 10.41 vs. 133.79 ± 11.81, 0.075) as well as diastolic BP (82.45 ± 11.49 vs. 79.59 ± 7.82, p=0.222) were not significantly different in increased and normal CIMT patients respectively. Among Diabetes parameters, fasting blood sugar (131.75 ± 26.35 vs. 119.59 ± 23.83, p=0.034), HbA1c (8.48 ± 0.91 vs. 8.05 ± 0.84, p=0.030) and duration of Diabetes (12.61 ± 5.23 vs. 7.62 ± 5.03, 0.0001) were significantly higher in increased CIMT patients compared to normal CIMT group whereas no significant difference was observed for post-prandial blood sugar (177.10 ± 34.31 vs. 162.34 ± 41.53, p=0.070) in two groups respectively.

Keywords: Risk factors, carotid intima media thickness, type-2 diabetes mellitus

Introduction

Diabetes mellitus (DM) is a fast growing non-communicable disease worldwide and also in India. Estimates of year 2000 depicted that India was the capital of Diabetes and ranked first with 31.7 million Diabetics. Worldwide prevalence of Diabetes is expected to double from 171 million (in the year 2000) to 366 million by 2030 [1].

A recent study by Indian Council of Medical Research (ICMR) reported that India currently has over 62.4 million individuals suffering from Diabetes and this is expected to increase over 100 million by 2030. More than 90% of the people had type 2 DM [2]. This increase in prevalence is not only restricted to developed part of the country but also rural population is equally affected.

A prevalence of 41.96% was reported in middle aged rural Indian population [3]. From the Unites States (US), 9.3% of people reported to have DM with around 27.8% of people with Diabetes being remained undiagnosed [4]. In South-East Asia region, Bangladesh, Indonesia and Thailand are behind India in that order in terms of number of people with Diabetes [4].

It is predicted that deaths due to Diabetes will rise by more than 50% in next 10 years and by 2030 Diabetes will become a seventh leading cause of death worldwide. 80% of Diabetic deaths have been reported from low-and middle-income countries [6].

A person with Diabetes is at risk of developing number of disabling and life threatening complications. These include cardiovascular disease, blindness, kidney failure, neuropathy, sleep apnoea and diabetic foot [7]. Older people with 6 or more co-morbid conditions are reported to have highest probabilities (>90%) of congestive heart failure (CHF) and myocardial infarction (MI) [8].

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The basic pathology that relates complications of Diabetes with blood sugar levels is atherosclerosis. The basic mechanism that is responsible for atherosclerosis in Diabetics is non-enzymatic reaction between glucose and proteins or lipoproteins in arterial walls. This ultimately leads to the formation of form Advanced Glycosylation End products (AGEs). Once formed, AGE-protein adducts are stable and virtually irreversible [9].

The degree of non-enzymatic glycation is determined mainly by the glucose concentration and time of exposure. Atherosclerosis promotion by AGEs occurs by nor-receptor mechanisms like changes in extracellular matrix (ECM), functional alterations in regulatory proteins and lipoprotein modifications as well as receptor mediated mechanisms like promotion of inflammation through cytokines, cellular proliferation induction and endothelial dysfunction [9].

Assessing latent atherosclerosis is difficult clinically. However a widely studied index of atherosclerosis that is shown to be associated with most risk factors of atherosclerosis is Intima-Media Thickness of arteries (IMT). Measuring IMT of extra-cranial carotid arteries (carotid IMT-CIMT) provides status of atherosclerosis in other vessels also [10].

Methodology

This single centre, prospective, observational study was carried out in Diabetes unit of tertiary care hospital in patients of type 2 Diabetes Mellitus (T2DM). After the approval of institutional ethics committee, Diabetic patients attending the Diabetology unit of a tertiary care centre were recruited into the study. Patients were screened with following inclusion and exclusion criteria and total 100 patients were enrolled in the study.

Inclusion criteria

- Age ≥ 18 years.
- Either gender.
- Diagnosed type 2 Diabetes Mellitus (T2DM).
- Willing to participate in the study.

Exclusion criteria

- Patients with type I DM.
- Secondary Diabetes.
- Overt renal failure.
- Congestive cardiac failure Urinary tract infection.
- Recent inter current illness.
- Pregnant females.
- Not willing to give informed consent.

Demographic and Other Relevant Clinical History

After initial screening, demographic details of the patient like patient identifier, age, gender, height, weight, smoking history, alcoholism history were recorded in case record form (CRF). Other relevant history like history of coronary artery disease (CAD), history of stroke or transient ischemic attacks (TIAs), history of peripheral arterial disease, autonomic neuropathy, retinopathy and renal disease was also noted in CRF.

Results

Table 1: Baseline characteristics of patients

Characteristic (N=100)	Value (Mean ± Std. deviation)
Age (years)	58.67 ± 7.07
BMI (Kg/m2)	26.34 ± 0.92
WHR	0.87 ± 0.03
SBP (mmHg)	136.84 ± 21.21
DBP (mmHg)	81.62 ± 12.73
Hb (gm %)	10.34 ± 1.41
Total cholesterol (mg/dL)	192.80 ± 0.00
Serum Triglycerides (mg/dL)	144.87 ± 21.21
Serum Creatinine (mg/dL)	01.60 ± 0.57
Carotid intima-media thickness (CIMT) (mm)	0.91 ± 0.01

Describes mean values of different characteristics of patients. Mean (±SD) age of the patients was 58.67 ± 7.07; mean body mass index was 26.34 ± 0.92, mean value of waist: hip ratio was 0.87 ± 0.03, mean

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systolic BP was 136.84 ± 21.21 and diastolic BP was 81.62 ± 12.73. Amongst blood investigation, mean hemoglobin was 10.34 ± 1.41, mean cholesterol was 192.80 ± 0.00, mean triglyceride levels were 144.87 ± 21.21, mean serum creatinine was 01.60 ± 0.57 and mean value of carotid intima-media thickness was 0.91 ± 0.01.

Table 2: Diabetes parameters in study patients

Parameters	Value (Mean ± SD)
Fasting Blood Sugar (mg %)	128.20 ± 19.80
Post-Prandial Blood Sugar (mg %)	172.82 ± 14.85
Glycated Hemoglobin (%)	8.36 ± 0.28
Duration of Diabetes (years)	11.16 ± 2.12

Describes the parameters related to Diabetes in patients enrolled. Mean values of fasting and post prandial blood sugar levels were 128.20 ± 19.80 and 172.82 ± 14.85 respectively. Glycated hemoglobin (HbA1c) mean level was 8.36 ± 0.28. Mean duration of Diabetes was 11.16 ± 2.12 years.

Table 3: Carotid intima thickness levels in study patients

CIMT (mm)	n (%)
≤ 0.90 (Normal)	29 (29.00%)
> 0.90 (increased)	71 (71.00%)

Represents groups of patients categorised based on CIMT level. There were 29.00% patients who had normal CIMT (≤ 0.90 mm) and 71.00% patients had increased CIMT (> 0.90 mm).

Table 4: CIMT association with different risk factors

Risk Factor	Increased CIMT	Normal CIMT	P value
Age	61.07 ± 7.73	52.79 ± 9.03	0.0001*
Gender (M/F)	36/35	14/15	0.826#
BMI	26.56 ± 2.25	25.80 ± 1.65	0.105
WHR	0.87 ± 0.05	0.85 ± 0.05	0.225
Smoking	25	8	0.462#
SBP	138.08 ± 10.41	133.79 ± 11.81	0.075
DBP	82.45 ± 11.49	79.59 ± 7.82	0.222
FBS	131.75 ± 26.35	119.59 ± 23.83	0.034*
PPBS	177.10 ± 34.31	162.34 ± 41.53	0.070
HbA1c	8.48 ± 0.91	8.05 ± 0.84	0.030*
Duration of Diabetes	12.61 ± 5.23	7.62 ± 5.03	0.0001*
Total cholesterol	198.03 ± 25.78	180.00 ± 22.99	0.001*
Serum TGs	149.03 ± 15.52	134.69 ± 16.05	0.0001*
Serum creatinine	1.67 ± 0.89	1.41 ± 0.75	0.162
UACR	121.17 ± 165.5	65.62 ± 131.9	0.111

*P<0.05, Independent sample t test

Chi square test

Mean age was significantly higher in patients with increased CIMT compared normal CIMT patients (61.07 ± 7.73 vs. 52.79 ± 9.03, p=0.0001) respectively. Overall increased CIMT was similar in males and females (36% vs. 35%). Mean BMI was not significantly different in two groups (26.56 ± 2.25 vs. 25.80 ± 1.65, p=0.105) as was the waist: hip ratio (0.87 ± 0.05 vs. 0.85 ± 0.05, p=0.225) respectively. More number of smokers had increased CIMT (25% vs. 8%, p=0.462). Systolic (138.08 ± 10.41 vs. 133.79 ± 11.81, 0.075) as well as diastolic BP (82.45 ±11.49 vs. 79.59 ± 7.82, p=0.222) were not significantly different in increased and normal CIMT patients respectively. Among Diabetes parameters, fasting blood sugar (131.75 ± 26.35 vs. 119.59 ± 23.83, p=0.034), HbA1c (8.48 ± 0.91 vs. 8.05 ± 0.84, p=0.030) and duration of Diabetes (12.61 ± 5.23 vs. 7.62 ± 5.03, 0.0001) were significantly higher in increased CIMT patients compared to normal CIMT group whereas no significant difference was observed for post-prandial blood sugar (177.10 ± 34.31 vs. 162.34 ± 41.53, p=0.070) in two groups respectively. In lipid parameters, total cholesterol (198.03 ± 25.78 vs. 180.00 ± 22.99, p=0.001) and triglyceride levels (149.03 ± 15.52 vs. 134.69 ± 16.05, p=0.0001) were significantly higher in increased CIMT group compared to normal CIMT respectively. Serum creatinine levels were not significantly different in two groups (1.67 ± 0.89 vs. 1.41 ± 0.75, p=0.162) as were levels of urinary albumin: creatinine ratio (121.17 ± 165.5 vs. 65.62 ± 131.9, p=0.111).

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Discussion

Overall mean CIMT was observed to be (0.91 ± 0.01) mm. This suggests majority of patients would have increased CIMT. This is well reflected in Diabetic parameters with mean FBS being (128.20 ± 19.80) mg/dl, mean PPBS being (172.82 ± 14.85) mg/dl, mean HbA1c being (8.36 ± 0.28) % and mean duration of Diabetes (11.16 ± 2.12) years, which also supports the increased CIMT levels in our patients. As discussed previously, CIMT is a well standardized surrogate marker for assessing cardiovascular risk and it is well accepted as a parameter of subclinical atherosclerosis. CIMT is a strong predictor of future cardiovascular events and is associated with conventional markers of cardiovascular risk such as age, hypertension and dyslipidemia. Studies have shown that in Asian Indians there is an association between increased CIMT and type 2 Diabetes, CIMT significantly higher in Diabetic patients than in non-Diabetic subjects. It has also been demonstrated that subclinical atherosclerosis increases with increasing degrees of glucose intolerance.

As regards to the CIMT levels, value 0f CIMT below 0.9 mm is considered as normal and any values 0.9mm and above are considered as increased which puts a person at higher risks of complications. In our study 71.00% patients had increased CIMT and 29.00% had normal CIMT. Similar results have been reported by Kalay *et al*. with 66.91% patients having increased CIMT in their study [11].

CIMT was increased in patients who had higher age and significant difference was observed compared to those patients who had normal CIMT (p=0.0001). Also there was strong positive correlation between age and CIMT (r=0.611, p=0.01). This stronger association suggests age increases the risk of increased CIMT and increasing age predisposes patients with Diabetes to increased CV risk. It has been reported that progression of CIMT is influenced by cardiovascular risk factors and is directly related to the risk of future cardiovascular events. No significant gender difference (p=0.826), was observed for CIMT levels suggesting both gender have equal chance of progression of CIMT with increasing age.

Body Mass Index is assessment tool for obesity. Mean BMI was in overweight range for all Diabetic patients. Though mean values of BMI were not significantly different in patients with normal and increased CIMT (p=0.105) a positive correlation was observed with BMI (r=0.079, p=0.437), Similar finding has been reported by Gayathri *et al*. with non-significantly higher BMI in patients with increased CIMT (0.9 or more) compared to normal CIMT (<0.9) (p=0.44) [12].

Waist Hip Ratio is a another index of obesity and risk factor for Diabetes. There was no significant difference for WHR in either patient with increased or normal CIMT but a positive correlation was observed (r=0.108, p=0.284). This suggests both BMI and WHR can have potential impact on development of CIMT in patients of Diabetes. In contrast to this Gayathri *et al*. reported a significant difference in WHR in patients with increased CIMT (p=0.03) [12].

Higher number of smokers had increased CIMT (25 out of 33,p=0.462). This predicts that smoking has adverse effects on endothelial function and can result in increased CIMT. Although some Indian studies have reported no association of smoking. Heavy smoking can affect glycemic levels and these can adversely affect CIMT through formation of AGEs [12].

Systolic and Diastolic blood pressure were in pre-hypertension range. Although mean values of SBP and DBP were not significantly different (p=0.075, p=0.222 respectively), in two groups, a significant positive correlation was observed with SBP (r=0.236, p=0.018) and positive but non-significant correlation with DBP (r=0.178, p=0.077). Studies have reported positive association between CIMT and hypertension [13]. Manios *et al*. in a multivariate linear regression analyses reported significant and independent associations of CIMT with daytime SBP (b=0.068; 95% CI, 0.034-0.102; P=001). Further they reported patients with isolated systolic (0.771 mm) and systolic/diastolic masked hypertension (MH) (0.775 mm) had significantly (p<0.05) higher CIMT values than those with isolated diastolic MH (0.664 mm) even after adjustment for baseline characteristics and risk factors [13]. Similarly, Gayathri *et al*. reported that 77.77% of those with hypertension had increased intima media thickness with a nearly significant (p value of 0.06) [12]. Thus highlighting importance of BP in development and progression of increased CIMT [14].

Conclusion

Most patients had increased CIMT levels. Increased CIMT was significantly found to be associated with age, smoking, fasting blood sugar levels, HbA1c levels, duration of Diabetes, total cholesterol levels, and serum triglyceride levels.

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