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A Study on the Risk Factors for Increased Carotid Intima Media Thickness (Cimt) in Type-2 Diabetes Mellitus

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Abstract

One of the important mechanisms responsible for the accelerated atherosclerosis in Diabetes is the non-enzymatic reaction between glucose and proteins or lipoproteins in arterial walls collectively known as Maillard or browning reaction. Glucose forms chemically reversible early glycosylation products with reactive amino groups of circulating or vessel wall proteins (Schiff bases) which subsequently re-arrange to form the more stable Amadori-type early glycosylation products. 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 center were recruited into the study. There was significant positive correlation of CIMT with age (Pearson Correlation coefficient: 0.611, $p<0.01$). But with BMI, though a positive correlation was observed, it was not significant (Pearson Correlation coefficient: 0.079, $p=0.437$). Similarly, with WHR (4C) positive correlation was observed but it was not significant (Pearson Correlation coefficient: 0.108, $p=0.284$).

Keywords: CIMT; BMI; Age.

Introduction

Both type I and type II Diabetes are powerful and independent risk factors for Coronary Artery Disease (CAD), stroke and peripheral arterial disease (PAD). Atherosclerosis accounts for virtually 80% of all deaths among North American Diabetic patients compared with one third of all deaths in the general North American population. More than 75% of all hospitalizations for Diabetic complications are attributable to cardiovascular disease.

Prolonged exposure to hyperglycemia is now recognized as the primary casual factor in the pathogenesis of Diabetic complications. Hyperglycemia induces a large number of alterations in vascular tissue that potentially promote accelerated atherosclerosis. Currently, three major mechanisms have emerged that encompass most of the pathological alterations observed in the vasculature of Diabetic animals and humans:

- Non-enzymatic glycosylation of proteins and lipids
- Oxidative stress
- Protein Kinase C (PKC) activation [1].

The effects of hyperglycemia are often irreversible and lead to progressive cell dysfunction. For example, in Diabetic patients with functioning pancreatic transplants renal pathology continues to progress for at least 5 years after Diabetes has been cured. The mechanism for these observations is unclear but suggests that cellular perturbations may persist despite the return of normoglycemia (memory effect). Thus, persistent rather than transient acute metabolic changes are of pivotal importance in the pathogenesis of Diabetic complications.

One of the important mechanisms responsible for the accelerated atherosclerosis in Diabetes is the non-enzymatic reaction between glucose and proteins or lipoproteins in arterial walls collectively known as Maillard or browning

reaction. Glucose forms chemically reversible early glycosylation products with reactive amino groups of circulating or vessel wall proteins (Schiff bases) which subsequently re-arrange to form the more stable Amadori-type early glycosylation products. Equilibrium levels of Schiffbase and Amadori products (the best known of which is Hemoglobin A1C) are reached in hours and weeks, respectively. Some of the early glycosylation products on long-lived proteins (e.g. vessel wall collagen) continue to undergo complex series of chemical re-arrangement to form Advanced Glycosylation End products [2].

Once formed, AGE-protein adducts are stable and virtually irreversible. Although AGEs comprise a large number of chemical structures, carboxymethyl-lysine-protein adducts are the predominant AGEs present in vivo. AGEs accumulate continuously on long-lived vessel wall proteins with aging and at an accelerated rate in Diabetes. The degree of non-enzymatic glycation is determined mainly by the glucose concentration and time of exposure. However, another critical factor to the formation of AGEs is the tissue micro-environment redox potential. Thus, situations in which the local redox potential has been shifted to favor oxidant stress, AGEs formation increases substantially. AGEs can accelerate the atherosclerotic process by diverse mechanism, which can be classified as non-receptor dependent and receptor-mediated [3].

The central pathological mechanism in macrovascular disease is the process of atherosclerosis which leads to narrowing of arterial walls throughout the body. Atherosclerosis is thought to result from chronic inflammation and injury to the arterial wall in the peripheral or coronary vascular system. In response to endothelial injury and inflammation, oxidized lipids from LDL particles accumulate in the endothelial wall of arteries.

Angiotensin II may promote the oxidation of such particles. Monocytes then infiltrate the arterial wall and differentiate into macrophages, which accumulate oxidized lipids to form foam cells. Once formed, foam cells stimulate macrophage proliferation and attraction of T-lymphocytes. T-lymphocytes in turn induce smooth muscle proliferation in the arterial walls and collagen accumulation.

The net result of the process is the formation of a lipid-rich atherosclerotic lesion with a fibrous cap. Rupture of this lesion leads to acute vascular infarction. In addition to atheroma formation, there is strong evidence of increased platelet adhesion and hypercoagulability in type 2 Diabetes. Impaired nitric oxide generation and increased free radical formation in platelets as well as altered calcium regulation may promote platelet aggregation. Elevated levels of plasminogen activator inhibitor type 1 may also impair fibrinolysis in patients with Diabetes. The combination of increased coagulability and impaired fibrinolysis likely further increases the risk of vascular occlusion and cardiovascular events in type 2 Diabetes. Among macrovascular diabetes complications coronary heart disease has been associated with Diabetes in numerous studies beginning with the Framingham study. More recent studies have shown that the risk of Myocardial Infarction (MI) in people with Diabetes is equivalent to the risk in non-Diabetic patients with a history of previous MI. These discoveries have lead to new recommendations by the ADA and AHA that Diabetes be considered a coronary artery disease risk equivalent rather than a risk factor [4].

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 center were recruited into 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 intercurrent illness
- Pregnant females
- Not willing to give informed consent

Results

As mentioned in Table 1, 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) (Table 1).

There was significant positive correlation of CIMT with age (Pearson Correlation coefficient: 0.611, p<0.01) as depicted in Figure 1. But with BMI, though a positive correlation was observed, it was not significant (Pearson Correlation coefficient: 0.079, p=0.437) (Figure 2). Similarly, with WHR (4C) positive correlation was observed but it was not significant (Pearson Correlation coefficient: 0.108, p=0.284) (Figure 3).

Table 1: CIMT association with different risk factors

Risk Factor	Increased CIMT	Normal CIMT	P value
Age	61.07	52.75	0.0001*
Gender (M/F)	36/35	14/15	0.826#
BMI	26.56	25.80	0.105
WHR	0.87 ± 0.05	0.85 ± 0.05	0.225
Smoking	25	8	0.462#
SBP	138.08	133.79	0.075
DBP	82.45	79.59	0.222
FBS	131.75	119.59	0.034*
PPBS	177.10	162.34	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	180	0.001*
Serum TGs	149.03	134.69	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

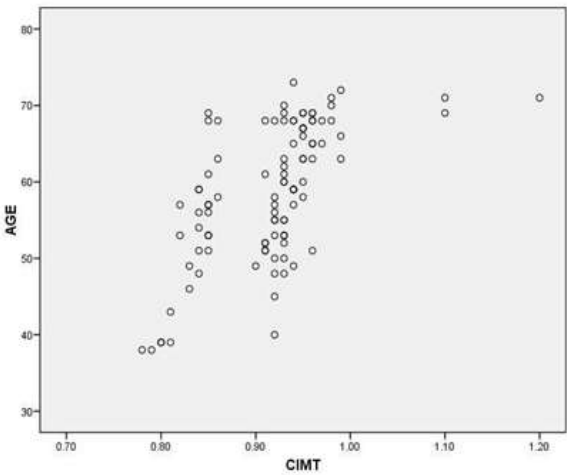

Fig. 1: Correlation between CIMT and Age

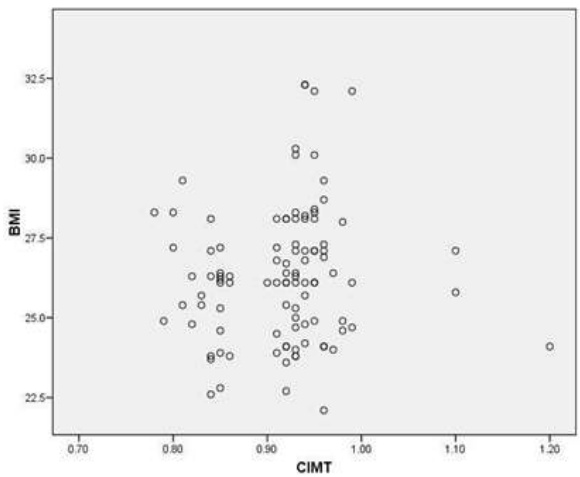

Fig. 2: Correlation between CIMT and BMI

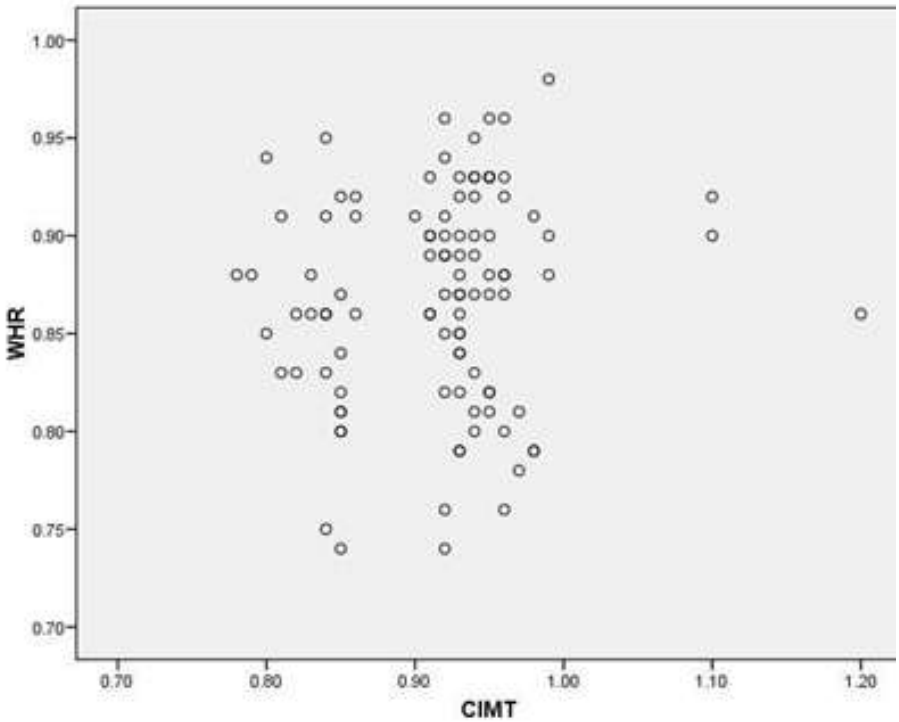

Fig. 3: Correlation between CIMT and Waist: hip ratio

There was significant positive correlation of CIMT with systolic BP (Pearson Correlation coefficient: 0.236, p=0.018) but with diastolic BP, though a positive correlation was observed, it was not significant (Pearson Correlation coefficient: 0.178, p=0.077).

There was significant positive correlation of CIMT with all three parameters of glycemia namely FBS (Pearson Correlation coefficient: 0.226, p=0.024), PPBS (Pearson Correlation coefficient: 0.223, p=0.026) and HbA1c (Pearson Correlation coefficient: 0.232, p=0.020). Also a significant positive correlation of CIMT with duration of Diabetes (Pearson Correlation coefficient: 0.656, p=0.0001) was observed.

Discussion

Asian Indians are known to have very high rates of Diabetes and premature coronary artery disease. For assessment of macro-vascular complications Carotid Intima-Media Thickness (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 [5].

Earlier studies have documented a significant role of CIMT in cardiovascular disease prediction in both non-Diabetic and Diabetic populations. 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 [6,7] and also demonstrated that subclinical atherosclerosis increases with increasing degrees of glucose intolerance. Thus CIMT assessment in relation to complications of Diabetes becomes necessary [8].

Traditional risk factors for associated with Diabetes include non-modifiable factors like age, gender, genetics, family history and modifiable factors like body mass index, physical inactivity, dietary factors, dyslipidemia and hypertension [9].

In 100 patients enrolled in this study, majority were in age range of 51 to70 years suggesting middle age onset or diagnosis of Diabetes in Indian patients. Mean age in present study was (58.67±7.07),. Presence of Diabetes in this age group poses higher risks ofcomplications with morbidity and mortality. Oldridge, et al. reported that in the middle-age group, the odds ratio (OR) for mortality in patients with a combination of obesity and Diabetes was 6.81

and it was 6.10 in those with a combination of heart disease and Diabetes. There also were significant OR for mortality in middle aged patients with heart disease (OR = 2.40), Diabetes (OR = 2.63) and for those with a combination of obesity, hypertension and Diabetes (OR = 3.26). Thus preventing such diseases may help reduce morbidity and mortality in middle aged and older adults [10].

It has also been reported that the incidence of Diabetes increases with age until about age 65 years, after which both incidence and prevalence seem to level off. As a result, older adults with Diabetes may either have incident disease (diagnosed after age 65 years) or long-standing Diabetes with onset in middle age or earlier [11].

There was no difference in number of males and females with Diabetes in our study. As regards to gender it has been observed that type 2 Diabetes showed a pronounced female excess in the first half of the last century but is now equally prevalent among men and women in most populations with some evidence of male preponderance in early middle age. Men seem more susceptible than women to the consequences of indolence and obesity. Possibly due to differences in insulin sensitivity and regional fat deposition. Women are however, more likely to transmit Type 2 Diabetes to their offspring [12].

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 associatedwith 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 [13,14].

As regards to the CIMT levels, value 0f CIMT below 0.9 mm is considered as normal and any values 0.9 mm 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 [15].

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 equalchance of progression of CIMT with increasing age.

Body Mass Index is assessment tool for obesity. Mean BMI was inoverweight range for all Diabetic patients. Though mean values of BMI werenot 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) [16].

Waist Hip Ratio is a another index of obesity and risk factor forDiabetes. 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) [16].

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 ofAGEs [16].

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 [17]. 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 [17]. 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) [16]. Thus highlighting importance of BP in development and progression of increased CIMT.

Conclusion

Strong positive correlation of CIMT was observed with age, systolic blood pressure, fasting and post-prandial blood sugar, HbA1c levels, duration of Diabetes, total cholesterol and serum triglyceride as well as with urinary albumin to creatinine ratio.

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