International Journal of Medicine Research
ISSN: 2455-7404
www.medicinesjournal.com
Volume 3; Issue 3; July 2018; Page No. 11-14

Relation of CIMT to various Micro & Macro-vascular complications of Diabetes

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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. 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. Mean values of CIMT in patients with and without macrovascular complications were non-significant for CAD [0.93 ± 0.04 vs 0.91 ± 0.06 (p=0.341)], CVA [0.92 ± 0.03 vs 0.91 ± 0.06 (p=0.691)], and PVD [0.93 ± 0.02 vs 0.91 ± 0.06 (p=0.225)] respectively. Glycemic parameters like FBS, PPBS, HbA1c and duration of diabetes were significantly associated with occurrence of retinopathy and nephropathy.

Keywords: CIMT, micro & macro-vascular complications, diabetes

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 [5].

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. 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) [6]. 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 [7].

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 [8].

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.

CIMT has been proposed as a risk factor that may be included in the algorithms for cardiovascular risk assessment. In CIMT measurement, common carotid and internal carotid arteries are usually taken into consideration. Considering this relative risk of MI is reported more with increasing internal CIMT compared with common CIMT, but the opposite is reported for stroke risk.

The risk of complications in a person varies with severity of CIMT. It has been reported that increased hazard ratios of the asymptomatic presence of increased CIMT have significantly increased hazard ratios for clinical end points like MI, stroke and CV death[8]. Beside this, considering other complications

of Diabetes like retinopathy, peripheral arterial disease, good amount of evidence suggests strong association between CIMT and risk of complications [8, 9].

Given the huge number of Diabetic population in our country, assessing CV risk in a Diabetic person becomes important. Correlation of CIMT with incident complications of Diabetes makes CIMT a useful screening test to be used clinically. This method provides cheap and safe alternative to other invasive and non-invasive tests.

Data on CIMT and complications of Diabetes especially related to retinopathy and PAD is sparse in Indian population where burden is high. So we planned this prospective study to assess CIMT in patients with Diabetes and further study its association with complications of Diabetes.

Methodology

Diabetic patients attending the Diabetology unit of a tertiary care center 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

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: Complications of Diabetes encountered in study

Complications	N	Percentage
Coronary Artery Disease	13	13.00%
Cerebrovascular Accident	7	07.00%
Peripheral Vascular Disease	16	16.00%
Retinopathy	33	33.00%
Neuropathy	19	19.00%
Nephropathy	32	32.00%

Among macrovascular complications, coronary artery disease, cerebrovascular accident and peripheral vascular disease were present in 13.00%, 7.00% and 16.00% of the patients. In microvascular complications, most common encountered complication was retinopathy (33.00%) followed by nephropathy and neuropathy in 32.00% and 19.00% patients respectively.

Table 2: Relationship between CIMT and complications of Diabetes

Complication	Increased CIMT	Normal CIMT	P value
Coronary Artery Disease	12	1	0.069
Cerebrovascular Accident	6	1	0.670
Peripheral Vascular Disease	15	1	0.034*
Retinopathy	28	5	0.032*
Neuropathy	16	3	0.159
Nephropathy	26	6	0.121

*P<0.05, Chi Square test (Fischer exact test)

Though all complications were common in patients with increased CIMT compare to normal patients, retinopathy (28 vs 5, p=0.032) and peripheral vascular disease (15 vs 1, p=0.034) were significantly more common with increased CIMT group of patients. Coronary heart disease (12 vs 1, p=0.069), cerebrovascular disease (6 vs 1, p=670), neuropathy (16 vs 3, p=0.159) and nephropathy (26 vs 6, p=0.121) were non-significantly more in patients with increase CIMT as compared to normal counterparts.

Table 3: Mean CIMT in patients with or without complications

Complications	CIMT (Mean ± SD)		P value
	Patient with Complications	Patient Without Complications	
CAD	0.93 ± 0.04	0.91 ± 0.06	0.341
CVA	0.92 ± 0.03	0.91 ± 0.06	0.691
PVD	0.93 ± 0.02	0.91 ± 0.06	0.225
Retinopathy	0.95 ± 0.07	0.89 ± 0.05	0.0001
Neuropathy	0.92 ± 0.04	0.91 ± 0.06	0.691
Nephropathy	0.94 ± 0.07	0.90 ± 0.05	0.001

Mean values of CIMT in patients with and without macrovascular complications were non-significant for CAD [0.93 ± 0.04 vs 0.91 ± 0.06 (p=0.341)], CVA [0.92 ± 0.03 vs 0.91 ± 0.06 (p=0.691)], and PVD [0.93 ± 0.02 vs 0.91 ± 0.06 (p=0.225)] respectively. For microvascular complications, significant difference for retinopathy [0.95 ± 0.07 vs 0.89 ± 0.05 (0.0001)] and nephropathy [0.94 ± 0.07 vs 0.90 ± 0.05, (p=0.001)] but not for neuropathy [0.92 ± 0.04 vs 0.91 ± 0.06, (p=0.691)] was observed respectively in patients with or without that complication.

Discussion

A review of 21 studies including 24,111 people with type 2 Diabetes and IGT found that CIMT was higher in individuals with Diabetes compared to the healthy controls. CIMT was increased in individuals with type 2 Diabetes by 0.13 (95% CI: 0.12–0.14) mm and by 0.04 (95% CI: 0.01–0.07) mm in individuals with IGT. Furthermore, CIMT has been demonstrated to be higher in people with Diabetes and macro-vascular disease. An Indian study in Diabetic subjects reported similar finding with 91% having increased carotid artery intima media thickness for duration of more than 15 years (p=0.020) [10].

In Chinese population, a study by Yang *et al*. reported mean of daily differences was predictor of CIMT in multiple linear regression analysis (r=0.346, p=0.005) suggesting glucose excursions may contribute to the development of atherosclerosis in patients with type 2 Diabetes which is

independent from HbA1c levels [11]. In another study conducted in Indian population by Arunkumar *et al*. compared CIMT in non-Diabetic and Diabetic population and reported a significant association between Diabetes and an increased incidence of abnormal CIMT. Further they observed higher HbA1c was positively associated with CIMT (P<0.001) [12].

Mohan V, *et al*. reported similar finding with significantly higher CIMT in Diabetic subjects compared to non-Diabetics. They also reported a significant correlation of duration of Diabetes with CIMT levels [13]. It has also been reported that in Asian Indians carotid IMT increases progressively with increasing severity of glucose intolerance and is also associated with the metabolic syndrome, independent of age and gender. Mechanisms that lead to alteration in vasculature because of high glycemic levels have been well described. Non-enzymatic glycosylation of proteins and lipids which can interfere with their normal function by disrupting molecular conformation alter enzymatic activity, reduce degradative capacity and interfere with receptor recognition. In addition, glycosylated proteins interact with a specific receptor present on all cells relevant to the atherosclerotic process including monocyte-derived macrophages, endothelial cells and smooth muscle cells. The interaction of glycosylated proteins with their receptor results in the induction of oxidative stress, pro-inflammatory responses and protein kinase C (PKC) activation with subsequent alteration in growth factor expression [9]. These findings highlights the importance of early diagnosis and prompt treatment of Diabetes in order to halt the progression of CIMT.

This has been the cornerstone for atherosclerosis. In present study, though the mean values of cholesterol and triglycerides were within normal reference range still the significant higher values were observed in patients with increased CIMT for total cholesterol (0.001) and serum triglyceride levels (0.0001). Also a strong positive correlation was observed between CIMT with total cholesterol (r=0.488, p=0.0001) and CIMT with TG levels (r=0.448, p=0.0001). This contrasts with report of Gayathri *et al*. who found no association between dyslipidemia and CIMT [37]. On the other hand, LDL-c (r = 0.325, P = 0.009) levels positively correlated and predicted CIMT in Diabetic individuals as reported by Yang *et al*. [11].

Complications of Diabetes are common occurrence and may vary according to the degree and duration of hyperglycemia. In present study, macro-vascular complications namely coronary heart disease, cerebrovascular disease and peripheral vascular disease were observed in 13.00%, 7.00% and 16.00% patients whereas micro-vascular complications namely Diabetic retinopathy, Diabetic neuropathy and Diabetic nephropathy were observed in 33.00%, 19.00% and 32.00% respectively. This shows huge burden of complications of Diabetes in Indian population. Occurrences of these complications were more common in patients who had increased CIMT and complications like PVD (15 vs 1, 0.034) and retinopathy (28 vs 5, 0.032) were significantly higher in patients with increased CIMT than those with normal CIMT. This probably suggests micro-vascular endothelial dysfunction starts early. Endothelial dysfunction has been reported to precede the development of atherosclerosis and is believed to play a central role in its pathophysiology. Impaired endothelial dependent vasodilatation exists in the presence of atherosclerosis. Endothelial dysfunction in the peripheral vessels are modestly correlated with the endothelial function in the coronary vessels [14].

Conclusion

Complications observed in Diabetic patients were retinopathy was the most followed by nephropathy, neuropathy, PVD, CAD and CVA. Retinopathy and PVD were significantly associated with increased CIMT. Significant difference in mean CIMT was observed in retinopathy and nephropathy patients.

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