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Observational Study

Correlating Carotid Intima-Media Thickness with Diabetic Retinopathy

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ABSTRACT

Background: Diabetes mellitus is one of the most common causes of end-stage renal disease, non-traumatic lower limb amputation and blindness. Furthermore, diabetic retinopathy (DR) is one of the most common causes of vision loss worldwide. The prevalence of DR increases with duration of diabetes and may even be present before a patient is diagnosed as a patient of diabetes mellitus. The risk factors of DR include poor glycaemic control, types of diabetes, dyslipidaemia and hypertension. Diabetes mellitus can also have macrovascular complications such as peripheral vascular disease and coronary artery disease which may lead to silent myocardial ischemia. A large number of diabetics with retinopathy may have an unidentified macrovascular disease. Carotid artery intima-media thickness (CIMT) is a sensitive marker of early carotid atherosclerosis, whereas DR is an early and reliable marker of microvascular complications of the disease.

Aim: The present study was carried out to study the correlation between carotid artery intima media thickness (CIMT) with risk factors for atherosclerosis and atherosclerotic events in type 2 diabetes mellitus patients. We also tried to find out the correlation between dyslipidaemia to DR in diabetic patients.

Materials and Methods: We included 25 diabetic patients of proliferative diabetic retinopathy (PDR), non-proliferative diabetic retinopathy (NPDR) and diabetics without DR, consecutively and they were divided in 3 groups along with 25 healthy volunteers. Thus, total 75 diabetic patients and 25 healthy controls were included in the study. Carotid IMT was evaluated using high-resolution B-mode ultrasonography. DR was graded and assessed using coloured fundus photography and fundus fluorescein angiography, as nonproliferative DR (NPDR) or proliferative DR (PDR). Simultaneously other routine investigations like fasting blood glucose (FBG), haemoglobin A1c (HbA1c) and lipid profile was also performed.

Results: Our study proves that both NPDR and PDR are strong determinants of carotid intima-media thickness (IMT) and atherosclerosis in patients with type 2 diabetes. CIMT shows a positive correlation with diabetes duration, fasting blood glucose, HbA1c, total cholesterol, triglycerides, LDL in PDR and NPDR patients while HDL is inversely correlated to it. Multiple regression analysis revealed that the determinants of CIMT in the studied group were duration of diabetes ($p<0.001$), triglycerides ($p<0.01$) and DR ($p<0.001$).

Conclusion: Our study proves that CIMT has a strong association with the severity of diabetic retinopathy.

Keywords: Diabetes, carotid intima media thickness, diabetic retinopathy, dyslipidaemia

Introduction

Diabetes mellitus affects vessels with many microvascular (diabetic retinopathy, nephropathy and neuropathy) and macrovascular complications (coronary artery disease, peripheral artery disease and stroke).[1] It has been observed that a large number of diabetics with retinopathy may have an unidentified macrovascular disease. Fioretto *et al*. observed that for the prevention of progression of vasculopathy early detection is needed.[2] Hernadez *et al*. suggested that true silent myocardial ischemia is a highly prevalent condition in type 2 diabetics especially in males and those with diabetic retinopathy (DR).[3] DR may be an independent risk marker for cardiovascular disease (CVD).[4]

Diabetic retinopathy is one of the most important causes of adult-onset vision loss worldwide.[5] Diabetes mellitus affects approximately 350 million people and one-third of these people will likely be affected by DR at some point.[6] The treatment of DR has improved, both medically and surgically, but it is still relatively difficult if it progresses to diabetic macular oedema (DMO) or proliferative DR (PDR), even for specialists.[7,8] DMO is often treated with anti-vascular endothelial growth factor (anti-VEGF), but the disease often recurs, and a significant proportion of patients do not respond to anti-VEGF, affecting clinical success.[9] Moreover, in neo-vascular glaucoma (NVG), which already has a relatively high prevalence of DMO after vitrectomy (approximately 10%), preoperative anti-VEGF therapy can be an additional risk factor.[10] Thus, the best strategy is preemptive treatment before DMO and PDR develop in patients with diabetes. This makes it important to find clinically useful new biomarkers of DR, as well as to understand the pathogenesis of DMO and PDR.[11] Poor glycaemic control, type of diabetes, and the presence of associated disorders such as dyslipidaemia, hypertension, smoking, pregnancy, and nephropathy are some other risk factors of DR development.[12-14] DR could present as non-proliferative retinopathy, proliferative retinopathy or macular oedema, however, the cause of visual loss among these patients is macular oedema, vitreous haemorrhage and tractional retinal detachment.[15,16] As a rule, DR precedes diabetic nephropathy, therefore, early detection of ocular manifestations of diabetes is important. DR presents 90% and 60% of type 1 and 2 diabetic patients, respectively.[17,18] Because the rate of progression of retinopathy is rapid and treatment can be beneficial for reduction of disease progression. There is a common pathophysiologic mechanism for the development of microangiopathy and macroangiopathy like advance glycation end products, oxidative stress, low-grade inflammation and neovascularization of vasa vasorum. The vascular complications due to atherosclerosis are a major cause of morbidity and mortality in type 2 diabetic patients, more so in India where the number of diabetics is approaching very high levels. Atherosclerosis which is the major risk factor is accelerated in diabetes mellitus. It has been suggested by the atherosclerotic risk project that the atherosclerotic process occurs at the same time in carotid, cerebral and coronary arteries. B mode ultrasonography can be used as a reliable tool for estimation of the intima-media thickness (IMT) of the carotid artery (CIMT). The American Heart Association (AHA) currently recommends arterial intima-media thickness measurement obtained by B mode as it is a relatively safer, non-invasive and inexpensive method of assessing subclinical atherosclerosis and an independent predictor of atherosclerotic events among various other non-invasive methods available. Thus, ultrasound CIMT measurement can be used as an assessment tool to predict cardiovascular risk and to determine indications for intensified diabetic treatment; on the other hand, DR is an early and reliable marker of microvascular disease.[19]

This study aimed to evaluate the relationship between retinopathy and CIMT as two valuable non-invasive methods for early detection of micro and macrovascular complication of diabetes.

Materials and Methods

The recruitment of study participants was done from the Department of Medicine, S.M.S Medical College, Jaipur, Rajasthan, India. 100 subjects were prospectively enrolled. Recruitment of candidates was done as per the recent guidelines by the AHA, 2018 and AACE, 2015. Consecutive 25 diabetic patients of PDR (group A1), NPDR (group A2) and without DR (group A3) were taken in 3 groups taking treatment from the Department of Medicine and 25 healthy controls were included in the study. Thus, a total of 75 diabetic patients and 25 healthy controls were included in the study.

Before participation in the study, written informed consent was taken and all study subjects were aged 40-75 years. Only those patients were included in this study who had a diabetes duration of 3 to 20 years, were normotensive (BP <135/85 mm Hg) and had a normal renal function. All subjects with deranged renal function, smokers and type 1 diabetes were excluded.

Statistical Analysis

The collected data were transformed into variables, coded and entered in Microsoft Excel sheet. Data obtained was analysed and statistically evaluated using SPSS-PC-17 version.

Quantitative data were expressed in mean, standard deviation and difference between comparable groups were tested by using ANOVA test or Kruskal-Wallis H test while qualitative data were expressed in percentage. Statistical differences between the proportions were tested by the chi-square test or Fisher's exact test. Correlation analysis was done using Pearson's correlation coefficient. A p-value of less than 0.05 was considered statistically significant.

Further, the odds ratio and 95% confidence interval was used to quantify the risk factors. Univariate analysis was done and among those factors which were found to be significant with $p \leq 0.1$ were entered in multivariate analysis.

Results

Table 1 shows the mean age in group A1 was maximum followed by group A2, group A3 and group B which is statistically not significant ($p>0.05$). Mean body mass index (BMI) in all patient groups (A1, A2, A3) was slightly higher as compared to control (group B) which is statistically not significant ($p>0.05$). Duration of diabetes was more in group A1 followed by group A2 and group A3 which is statistically significant ($p=0.01$). Mean fasting blood glucose and HbA1c were maximum in group A1 followed by group A2, group A3 and group B which was statistically significant ($p<0.01$). Mean serum total cholesterol, mean serum triglycerides and mean serum low-density lipoprotein (LDL) levels were maximum in group A1 followed by the group A2, group A3 and group B which were statistically significant ($p<0.001$). Mean serum high-density lipoprotein HDL was maximum in group A3 followed by group B, group A1 and group A2 which was statistically significant ($p<0.001$). Mean CIMT was maximum in group A1 followed by group A2, group A3 and group B which statistically significant ($p<0.001$).

These observations show that the development of DR is related to the duration of diabetes. The observations also suggest that poorer control of diabetes is associated with more severe form of diabetic retinopathy. High serum cholesterol, hypertriglyceridemia and higher LDL levels are associated with a more severe form of diabetic retinopathy while HDL is inversely correlated to it. This shows likely association of CIMT to the severity of diabetic retinopathy.

Table 1. Results for the different diabetic groups and control group with the comparison. Abbreviations: BMI- Body mass index; FBS- Fasting blood sugar; HbA1c- Haemoglobin A1c; TG- Triglyceride; HDL- High-density lipoprotein; LDL- Low-density lipoprotein; CIMT- Carotid artery intima-media thickness; PDR- Proliferative diabetic retinopathy; NPDR- Non-proliferative diabetic retinopathy; DR- Diabetic retinopathy.

Variables	Group A			Group B (Control) (n=25)	p-value
	PDR (A1) (n=25)	NPDR (A2) (n=25)	No DR (A3) (n=25)		
Age (years)	60.80±6.1	57.6±6.2	52.72±6.41	52.1±6.49	0.07
BMI (kg/m^2)	24.68±2.82	23.51±2.74	25.16±3.06	22.98±2.90	0.14
Diabetes duration (years)	10.52±3.01	8.52±2.71	6.92±1.80		0.01
FBS (mg/dL)	244.80±40.14	213.36±35.60	179.40±33.31	88.08±6.42	<0.01
HbA1c (%)	10.60±1.44	9.78±1.38	8.76±1.03	4.98±0.33	<0.01
Serum total cholesterol (mg/dL)	235.36±11.59	197.52±16.66	178.00±13.56	167.44±10.44	<0.001
Serum TG (mg/dL)	177.48±8.90	153.68±9.30	128.12±6.91	119.52±14.33	<0.001
Serum HDL (mg/dL)	39.72±3.51	34.76±4.34	42.56±3.41	40.92±4.66	<0.001
Serum LDL (mg/dL)	142.88±8.86	121.12±9.40	102.64±12.00	81.32±8.11	<0.001
Mean CIMT (mm)	0.89±0.06	0.77±0.06	0.68±0.01	0.53±0.03	<0.001

Table 2. Correlation between CIMT and other variables in different diabetic groups and control group. Abbreviations: BMI- Body mass index; FBS- Fasting blood sugar; HbA1c- Haemoglobin A1c; TG- Triglyceride; HDL- High-density lipoprotein; LDL- Low-density lipoprotein; CIMT- Carotid artery intima-media thickness; PDR- Proliferative diabetic retinopathy; NPDR- Non-proliferative diabetic retinopathy; DR- Diabetic retinopathy.

Variables	CIMT			
	PDR (A1)	NPDR (A2)	No DR (A3)	Control (Group B)
Age	0.73	0.06	0.28	0.18
BMI	0.96	0.44	0.59	0.69
FBS	<0.01	0.04	0.27	0.48
HbA1c	<0.01	0.03	0.28	0.13
Serum total cholesterol	<0.01	0.01	0.45	0.84
Serum TG	<0.01	0.03	0.53	0.95
Serum HDL	<0.01	0.02	0.94	0.35
Serum LDL	<0.01	0.01	0.17	0.13

Correlation analysis was done using Pearson's correlation coefficient. **Table 2** shows age and BMI were not significantly correlated with CIMT in patients of diabetic retinopathy (A1, A2, A3) and control (group B) ($p>0.05$). FBS and HbA1c were significantly correlated with carotid intima-media thickness in A1 and A2 groups ($p<0.05$) while the correlation was not significant in diabetes without retinopathy group and control group ($p>0.05$). These observations also suggest that the poorer control of diabetes is associated with the development of DR.

Lipid profiles were significantly correlated with carotid intima-media thickness in PDR (A1) and NPDR (A2) group while the correlation was not significant in diabetes without retinopathy group (A3) and control (group B).

These observations suggest that higher total cholesterol, triglycerides and LDL levels are associated with severity of DR, while HDL is inversely correlated to it.

Table 3. Association of CIMT with diabetic retinopathy after individually adjusting for different risk variable. Abbreviations: DM- Diabetes mellitus; BMI- Body mass index; FBS- Fasting blood sugar; HbA1c- Haemoglobin A1c.

Variable	Odds ratio	95% CI	p-value
Age	3.82	2.57-5.95	<0.001
Duration of DM	3.11	1.68- 4.87	0.002
BMI	2.36	1.10-5.02	0.013
FBS	2.66	1.09-5.56	0.03
HbA1c	2.33	1.11-4.88	0.02
Serum total cholesterol	1.06	1.02-1.14	0.006
Serum triglycerides	1.88	1.07-3.33	0.02

Logistic regression analysis was also done in our study using diabetic retinopathy as the dependent variable and carotid IMT as the independent variable. The odds ratios were determined after individually adjusting for the variables (**Table 3**). While analysing for age, duration of type 2 diabetes, BMI, fasting blood glucose, HbA1c, total cholesterol and triglycerides, chances of CIMT was 3.82 times, 3.11 times, 2.36 times, 2.66 times, 2.33 times, 1.06 times and 1.88 times higher in patients of diabetic retinopathy compared to patients of diabetes without retinopathy, respectively.

To evaluate the relative influence of several variables on the prevalence of retinopathy, we did multiple logistic regression analysis. These models are used to test the significance of variables in predicting the presence of retinopathy when the effects

of other variables are being considered. Multiple regression analysis was done to detect the determinants of CIMT in the study group (**Table 4**). These determinants were found to be the duration of diabetes ($p<0.001$), triglycerides ($p<0.01$) and diabetic retinopathy ($p<0.001$).

Table 4. Determinants of CIMT in the study group (multiple regression analysis). Abbreviations: BMI- Body mass index; SBP- Systolic blood pressure; DBP- Diastolic blood pressure; FBS- Fasting blood glucose; HbA1c- Haemoglobin A1c; TC- Total cholesterol; TG- Triglyceride; DR- Diabetic retinopathy.

Variable	Carotid Intima Media Thickness (p-value)
Age	Non-significant
BMI	Non-significant
Duration of diabetes	<0.001
SBP	Non-significant
DBP	Non-significant
FBS	Non-significant
HbA1c	Non-significant
TC	Non-significant
TG	<0.01
DR	<0.001

Discussion

Type 2 diabetes exposes the vasculature to the onslaught of several factors, mainly hyperglycaemia, hypertension, dyslipidaemia, haemostatic changes and inflammation. Epidemiologic studies have found that for every increase in maximum CIMT by 0.1 mm is associated with an 11% increase in the risk of myocardial infarction.[20,21] By comparing various groups, the mean CIMT in group A1 was 0.89±0.06 mm; in group A2 was 0.77±0.06 mm; in group A3 was 0.68±0.01 mm and group B was 0.53±0.03 mm. When mean CIMT of group A1, A2 and A3 were compared with control (group B) individually i.e., group A1 vs. B, group A2 vs. B, group A3 vs.B; all three p-values were found to be less than 0.001 ($p<0.001$).These indicate that the severity of diabetic retinopathy is associated with increased CIMT. These results are in concordance with study by Aasem Saif *et al*. in which they revealed that CIMT was significantly greater in patients with PDR compared to those with NPDR (1.094±0.142 mm vs. 0.842±0.134 mm; $p<0.001$).[22] Therefore, our observations are similar to previous studies that demonstrate CIMT as a marker of atherosclerosis and it strongly correlates with the severity of retinopathy.

Mean values of total cholesterol, triglycerides and LDL values are significantly higher when severity of DR increases as from diabetic without retinopathy to PDR. Low HDL values were associated with the severity of DR. In a study done by Yun YW *et al*., the mean levels of serum triglycerides in patients with retinopathy was 145.7 mg/dL and without retinopathy was 153.0 mg/dL.[23] The same study showed mean levels of serum HDL in patients with retinopathy was 47.7±12.7 mg/dL and without retinopathy was 47.3±11.1 mg/dL. Above findings suggest that all the lipid parameter correlates with the severity of diabetic retinopathy.

The individual p-value is calculated between group A1 and control group, group A2 and control group and group A3 and control group. Age and BMI were not significantly correlated with CIMT in patients of diabetic retinopathy (A1, A2, A3) and control (group B) ($p>0.05$). FBS and HbA1c were significantly correlated with carotid intima-media thickness in A1 and A2 groups ($p<0.05$) while the correlation was not significant in diabetes without retinopathy group and control group ($p>0.05$). These observations suggest the poorer control of diabetes is associated with the development of DR.

Lipid profiles were significantly correlated with carotid intima-media thickness in PDR (A1) ($p<0.01$) and NPDR (A2) ($p<0.05$) group while the correlation was not significant in diabetes without retinopathy group (A3) and control (group B). These observations suggest that higher total cholesterol, triglycerides and LDL levels are associated with severity of DR, while HDL is inversely correlated to it.

Aasem Saif *et al*. reported that CIMT was positively correlated with diabetes duration ($p<0.01$), FBS ($p<0.01$), HbA1c ($p<0.01$), total cholesterol ($p<0.01$) and triglycerides ($p<0.001$) in type 2 diabetic patients.[22]

While analysing for age, duration of type 2 diabetes, BMI, fasting blood glucose, HbA1c, total cholesterol, triglycerides chances of CIMT was 3.82 times, 3.11 times, 2.36 times, 2.66 times, 2.33 times, 1.06 times, 1.88 times higher in patients of diabetic retinopathy compared to patients of diabetes without retinopathy, respectively. In a similar study by Rema M *et al*., they also determined the odds ratio after individually analysing for the variables and observed a similar level of findings.[24]

Determinants of CIMT were found to be duration of diabetes ($p<0.001$), triglycerides ($p<0.01$) and DR ($p<0.001$). In a similar study done by Aasem Saif *et al*., after multiple regression analysis determinants of CIMT were found to be age ($p<0.01$), triglycerides ($p<0.001$) and DR ($p<0.0001$).[22] Most of the studies in the literature found a correlation between CIMT and duration of diabetes and age.[25]

The regression analysis in our study has proved that retinopathy itself is a very strong independent risk factor for CIMT and therefore, atherosclerosis, in patients with type 2 diabetes.

Conclusion

India currently has the largest number of diabetic patients in the world and these numbers are still rising. This rapid increase is attributed to the epidemiological transition occurring in India. Improvement in screening methods and increased awareness among the general population has increased number of cases detected. However, atherosclerotic and microvascular complications have increased with the increase in prevalence in type 2 diabetes and improved survival rate. Measurement of carotid artery intima-media thickness by non-invasive B mode ultrasonography can detect atherosclerosis at an early preclinical stage and help in the diagnosis of asymptomatic cardiovascular disease. CIMT was found to be increased among PDR patients as compared to NPDR and diabetic patients without retinopathy. The study of type 2 diabetic subjects showed that CIMT had a strong association with severity of diabetic retinopathy, duration of diabetes and triglycerides even after adjusting for age, fasting blood glucose and HbA1c, suggesting that common pathogenic factors might contribute to the development of both micro and macrovascular complications of diabetes mellitus. We also concluded that retinopathy is a multifactorial microvascular complication, which, apart from hyperglycaemia, is associated with dyslipidaemia. We found that higher total cholesterol, triglycerides and LDL levels are associated with severity of DR, while HDL has an inverse correlation to it.

Declaration of conflicting interests

The authors declare no conflict of interest.

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Ethical approval

Since this study is an observational study, there is no need of ethics committee approval.

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