CAROTID ATHEROSCLEROSIS AND PERIPHERAL VASCULAR DISEASE IN TYPE 2 DIABETES MELLITUS PATIENTS WITH CORONARY ARTERY DISEASE

Neetu Agarwal[1], Rajashree Khot[2], Sachin Jaybhaye[3], Vinayak Sawardekar[4], Ramkumar Soni[5], Chandan Bansal[6]

[1]*Associate Professor, Department of Medicine, Grant Govt. Medical College, Mumbai.*
[2]*Associate Professor, Department of Medicine, Indira Gandhi Medical College, Nagpur.*
[3]*Assistant Professor, Department of Medicine, Grant Govt. Medical College, Mumbai.*
[4]*Associate Professor, Department of Medicine, Grant Govt. Medical College, Mumbai.*
[5]*Assistant Professor, Department of ENT, Grant Govt. Medical College, Mumbai.*
[6]*Assistant Professor, Department of Medicine, Hi-Tech Hospital, Rourkela, Orissa.*

ABSTRACT

BACKGROUND
Patients with Type 2 Diabetes Mellitus (DM) suffer from premature severe atherosclerosis and can have multivascular involvement.
Aims and Objectives- To determine the prevalence of Carotid Atherosclerosis (CA) and Peripheral Vascular Disease (PVD) in Type 2 DM patients with coronary artery disease. To correlate multivascular morbidity with risk factors.

MATERIALS AND METHODS
In cross-sectional hospital-based study, 120 consecutive patients of Type 2 DM with CAD underwent Doppler studies and prevalence of CA or PVD was determined as per IMT, plaques and luminal stenosis. Macrovascular multimorbidity defined as presence of CA or PVD or both along with CAD. They were assessed for risk factors. Patients were divided into 2 groups: Group I- CAD alone, Group II- Multivascular morbidity. Comparisons were made using student 't' test and chi-square for univariate analysis and multivariate analysis done finally.

RESULTS
Mean age of patients was 56.17 + 7.8 years with M:F = 1:1. Of 120 patients 71 (59.1%) had CA (p=0.001), 40 (33.3%) had PVD (p=0.732) and 28 (23.3%) had both CA and PVD. Of 71 with CA 37 (52.11%) had increased IMT, 34 (47.88%) had plaques/luminal stenosis. Of 40 with PVD, 33 (82.5%) had increased IMT, 7 (17.5%) had plaques/stenosis. On univariate analysis male sex, age, duration of diabetes, hypertension, elevated fasting blood glucose and HbA1c, high LDL and low LDL were significantly associated with multivascular involvement. On multivariate analysis age, duration of diabetes, HbA1c were independent risk factors for multivascular involvement.

CONCLUSION
There is significantly high prevalence of macrovascular multimorbidity in Type 2 DM patients with CAD, more commonly in males. It is more with increasing age, Diabetes duration, Hypertension, uncontrolled DM and dyslipidaemia.

KEYWORDS
Type 2 DM, Coronary Artery Disease, Macrovascular Multimorbidity (CA and PVD).

BACKGROUND
Diabetics are more prone to advanced atherosclerosis and its sequelae namely Coronary Artery Disease (CAD), cerebrovascular disease, aortic atherosclerosis and peripheral vascular disease. Coronary Angiography (CAG) has been considered as the gold standard for the assessment of the degree of coronary atherosclerosis. But angiographic assessment of the coronary arteries is expensive, needs tertiary care hospitals and expertise and is not without risk.

Since atherosclerosis is a generalised phenomenon and is more or less present equally in the coronary, cerebral and the carotid arteries; so ultrasonographic assessment of easily accessible arteries has been advocated as a surrogate marker for less accessible vessels, such as coronary and cerebral arterial systems.

Carotid IMT (CIMT) has been shown to be independently associated with CAD in Indian subjects.[1,2] Therefore, the present study was planned to generate more data on this subject with the aim of measuring atherosclerotic changes in carotid arteries and in peripheral arteries in Type 2 Diabetes Mellitus (T2DM) with CAD and to correlate them with various known coronary risk factors.

Aims and Objectives
Primary
To determine the prevalence of carotid atherosclerosis and peripheral vascular disease by Doppler studies in patients of Type 2 diabetes mellitus with coronary artery disease.

Secondary

To correlate the multivascular morbidity in T2DM patients with cardiovascular risk factors like age, smoking, lipid profile, hypertension, duration of diabetes, etc.

MATERIALS AND METHODS

This cross-sectional hospital-based study included 120 patients of Type 2 diabetes mellitus (newly detected or on treatment) with coronary artery disease as diagnosed by Electrocardiography (ECG), Treadmill Stress Test (TMT) or Coronary Angiography (CAG). Diagnosis of type 2 diabetes was made based on blood sugar fasting and post-meal according to WHO criteria. Diagnosis of coronary artery disease was confirmed by presence of any one of these criteria:

i) ST-T changes, suggestive of ischaemia with anginal chest pain.
ii) Old Myocardial Infarction (MI).
iii) Recent MI.
iv) Positive TMT.
v) CAD as confirmed by CAG.

Diagnosis of Carotid Atherosclerosis was diagnosed by Doppler done on Aloka 4000 Prosound machine by presence of any one or more of the following-

i) Increased Intima Media Thickness (IMT) > 0.8 mm.
ii) Presence of plaque: fibrofatty or calcific.
iii) Presence of stenosis, i.e. > 50% luminal narrowing.

Diagnosis of Peripheral Vascular Disease was diagnosed by Doppler by presence of any one or more of the following-

i) Increased IMT > 1 cm.
ii) Presence of plaque.
iii) Presence of stenosis, i.e. luminal narrowing > 50%.

Multivascular morbidity was defined as presence of carotid atherosclerosis or peripheral vascular disease or both along with coronary artery disease. Type I diabetes mellitus, patients with age < 31 and > 65 years and having other associated causes of PVD and carotid atherosclerosis (like Takayasu's arteritis, Aortoarteritis, etc.) were excluded from the study. Each patient underwent detailed clinical history, physical examination and relevant laboratory investigations. Patients were divided into 2 groups for comparison, i.e. those patients with coronary artery disease alone and those with multivascular morbidity. Statistical analysis of data as per protocol was performed.

Statistical Analysis

Patients were divided into 2 groups for comparison, i.e. those patients with coronary artery disease alone and those with multivascular morbidity. All values were expressed as mean ± SD or as percentages. Statistical analysis was performed by using "SPSS - version 15" on personal computer. Statistical analysis included the usual descriptive and univariate analysis. Student 't' test was used to compare continuous variables. For categorical variables, chi-square test was used and 95% Confidence Interval (CI) along with 'p' value was calculated. A P value < 0.05 was considered as statistically significant. In addition to usual descriptive and univariate analysis, multivariate analysis was also made.

RESULTS

In the present study, a total of 120 type 2 diabetes mellitus patients attending diabetes clinic/indoor cases were included. Majority of patients (47.5%) were in age group 60 - 65 years. Mean age of patients was 56.17 ± 7.88 years and male: female ratio was 1:1. Out of the 120 patients, 37 i.e. 30.8% had normal carotid and peripheral arterial Doppler, while 71 patients (59.1%) had carotid atherosclerosis along with Coronary Artery Disease (CAD). This was statistically significant (p= 0.001) (Table 1); 40 patients (33.3%) had peripheral arterial disease along with CAD, but this was statistically insignificant (p= 0.732).

Out of 71 patients with carotid atherosclerosis, 37 (52.11%) patients had increased Intima-Media Thickness. Mean Intima-Media Thickness was found to be 1.04 mm; 30 patients (42.25%) had plaque, out of which 18 (25.35%) had fibrofatty plaque and 12 (16.9%) had fibrocalcific plaque; 4 patients (5.63%) had stenosis with haemodynamic compromise. Out of 40 patients with peripheral vascular disease 5 (12.5%) had atherosclerotic plaque, while 2 (5%) patients had stenosis with haemodynamic compromise. Rest of the patients had diffuse atherosclerotic changes in the form of increased Intima-Media Thickness. The mean age in the group who had CAD alone was 53.05 ± 9.64 years, while in the group who had CAD, carotid atherosclerosis and PVD mean age was 59 ± 5.75 years. This difference in age was statistically significant (p < 0.001). As the age increased, multivascular involvement increased. Single macrovascular involvement in the form of CAD alone was more frequent in female, i.e. 40% as compared to 21.7% in males. This difference was statistically significant (p = 0.03). However, multivascular involvement was more prevalent in males 78.33% as compared to 60% in females. This difference was also statistically significant (p = 0.024). Mean duration of diabetes in patients with single macrovascular involvement, i.e. CAD alone was 3.22 ± 4.3 years, while in those with multivascular involvement was 6.45 ± 5.25 years. The difference was statistically significant (p = 0.001). Hence, as duration of diabetes increase, multivascular involvement increased (Table 2). Mean fasting blood sugar in the group with multivascular involvement was high compared to those with CAD alone (p = 0.012). Mean HDL was low and mean LDL was high in the group with multivascular involvement compared to those with CAD alone (P value 0.002 and < 0.001, respectively). Amongst other risk factors, hypertension was found to be significantly associated in the group with multivascular involvement (Table 3).

Macrovascular Involvement	No. of Patients	P value
CAD Alone	37 (30.8%)	
CAD + CA	43 (35.8%)	0.001
CAD + PVD	12 (10%)	0.732
CAD + CA + PVD	28 (23.3%)	0.013
Total	120	
Table 1. Macrovascular Multi-Morbidity in Type 2 Diabetes Mellitus		

Duration of DM (Years)	CAD Alone	Multivascular Morbidity		
		CAD + CA	CAD + PVD	CAD + CA + PVD
0 – 5	30 (42%)	24 (34%)	7(10%)	10 (14%)
6 – 10	4 (12%)	13 (39%)	4(12%)	12 (36%)
11 – 15	2 (17%)	3 (25%)	1 (8%)	6 (50%)
> 15	1 (25%)	3 (75%)	-	-
Mean	3.22 ± 4.3	6.45 ± 5.25		
Total	37	43	12	28

Table 2. Correlation of Duration of Diabetes and Multivascular Involvement

Risk Factors		CAD Alone	CA	PVD	CAD + CA + PVD	Total	P value
Hypertension		28 (33%)	30 (36%)	6 (7%)	20 (24%)	84	0.001
Smoking		4 (21%)	6 (32%)	4 (21%)	5 (26%)	19	0.901
Alcohol		1	3	1	1	6	0.572
Dyslipidaemia		24 (29%)	33 (40%)	8 (9%)	18 (22%)	83	0.001
Family History	DM	1	3	1	1	6	0.446
	HT	-	2	1	-	3	
	CAD	2	1	1	-	4	

Table 3. Risk Factors and Association with Multivascular Morbidity

Multivariate regression analysis (Table 4) suggested that increasing age, increasing duration of diabetes and male sex had more prevalence of multivascular morbidity. Fasting blood sugar, hypertension and dyslipidaemia were not found to be independent predictors of multivascular morbidity, although they were significant risk factors on univariate analysis.

Variable	CAD Alone (n = 37)	Multivascular Morbidity (n = 83)	P value
Age (mean)	53.05 ± 9.64	58.16 ± 6.55	0.025
M:F	1:1.18	1.3:1	0.009
Hypertension	28	56	0.248
Mean Duration of DM	3.22 ± 1.3	6.45 ± 5.25	0.015
Mean FBS	141.13 ± 26.76	160.47 ± 42.5	0.144
Mean HbA1c	7.62 ± 0.64	8.85 ± 1.42	0.011
Mean HDL	39.92 ± 4.71	36.98 ± 4.62	0.791
Mean LDL	119.47 ± 34.94	146.14 ± 35.6	0.248

Table 4. Multiple Regression Analysis

Variable	B (Beta Adjusted Odds)	S. E. (Std. Error)	Wald	df (Degree of Freedom)	Significance	Exp.
Age	0.038	0.030	4.990	1	0.025	1.070
Sex	1.296	0.495	6.849	1	0.009	3.654
Duration of Diabetes	0.148	0.061	5.883	1	0.015	1.160
FBS	0.010	0.007	2.130	1	0.144	1.010
HDL	- 0.17	0.51	0.118	1	0.731	0.983
LDL	0.002	0.007	0.070	1	0.791	1.002
Hypertension	0.607	0.525	1.336	1	0.248	1.834

DISCUSSION

Patients with diabetes mellitus are at an increased risk of morbidity and mortality from macrovascular disease manifesting as Coronary Artery Disease (CAD), Cerebrovascular Accident (CVA) and Peripheral Vascular Disease (PVD). Increased frequency of dyslipidaemia, hyperglycaemia, obesity, hypertension and associated nephropathy may contribute to accelerated atherogenesis in diabetic patients. A non-invasive technique of assessing carotid atherosclerosis or peripheral arterial disease by 2D Doppler duplex scanning has generated considerable interest as a marker of atherosclerosis and in the prediction of clinical coronary events and coronary artery disease, especially in resource limited country like India. The present study is an example of evidence-based medicine in correlating multiple vascular beds, coronary, carotid and peripheral which share the same atherosclerotic risk factors. The primary aim of this study was to determine the prevalence of CA and PVD in type 2 DM patients who already had evidence of atherosclerosis in the form of coronary artery disease.

Similar to our study AK Agarwal, PK Gupta, et al[3] showed that the mean carotid IMT was significantly higher (p<0.0001) in Type 2 diabetics with CAD (Both overt and silent) than in those without CAD. Mudríková T et al[4] also found significantly increased Intima-Media thickness of the distal common carotid artery in patients with coronary artery disease. Kasliwal RR et al[5] also concluded from their study that both the mean and maximum carotid IMT were significantly higher in CAD group as compared to the non-CAD group.

The study conducted by Sodhi HS, Shrestha SK, et al[6] recommended that ABI as measured by sphygmomanometer be incorporated into routine cardiovascular screening and when found to be abnormal should be further confirmed by Doppler assessment of ABI and CCA IMT as surrogate markers of atherosclerotic vascular disease. In contrast to this the present study showed 33.3% (40 patients) had peripheral arterial disease in association with CAD, which was statistically insignificant (p = 0.732).

Prevalence of CA + PVD in CAD has not been determined in any study so far. Hence, we would like to report this fact, further substantiating the theory of accelerated atherogenesis in Type 2 diabetics leading to multivascular involvement. Thus, it can be said that multivascular involvement is more prevalent in Type 2 DM with CAD and that carotid atherosclerosis is more prevalent than peripheral vascular disease in diabetics with coronary artery disease. Few patients also have atherosclerotic involvement of all major vessels, i.e. carotid, femoral and coronaries.

The correlation of increasing age with carotid atherosclerosis was comparable with study conducted by KP Paulose,[7] who also showed a strong positive correlation with increasing age. Multivariate regression analysis proved that age and diabetes were the major risk factors for increased IMT.

Multivariate logistic regression analysis in this study had shown that the risk for carotid artery disease is 5-fold in patients with diabetes of more than 15 years duration (95% CI 2.0-17.1 p= 0.0003) as compared to those with less than 5 years duration. KP Paulose[7] showed comparable results and found a strong positive correlation between the duration of the disease and the incidence of carotid atherosclerosis.

In the present study, mean fasting blood sugar in the patients with CAD alone was 141.13 mg/dL, while it was 160.47 mg/dL in patients with multivascular morbidity, which was statistically significant. Study conducted by Martens FM, Van Der Graaf Y, et al[8] also showed that from all the components of the metabolic syndrome only high blood pressure and high fasting glucose influenced the carotid artery stiffness.

In our study, high LDL and low HDL were significantly associated with multivascular morbidity in univariate analysis. However, on multivariate analysis, multivascular involvement in diabetics was found to be independent of dyslipidaemia. This is because various mechanisms of increased atherosclerosis apart from dyslipidaemia are proposed in diabetics. These include oxidative stress, toxic effect of hyperglycaemia, endothelial dysfunction, etc. Rituparna Maiti et al[9] studied the concept of inflammation in diabetes-accelerated atherosclerosis and proposed inflammatory mechanisms coupled with dyslipidaemia in the process of atheroma formation in diabetics.

CONCLUSION

It was a cross-sectional study, carried out to determine the prevalence of carotid atherosclerosis and peripheral vascular disease by Doppler studies in patients of Type II diabetes mellitus with coronary artery disease and to correlate the multivascular morbidity in these patients with risk factors like age, smoking, lipid profile, hypertension, duration of diabetes, etc.

We concluded that-

1) 83 patients out of 120 had multivascular morbidity, which was statistically significant high prevalence of macrovascular multimorbidity in Type 2 DM patients with CAD.

2) Multivascular involvement was more prevalent in males, i.e. 78.33% as compared to 60% in females. This difference was statistically significant.

3) The mean age in the group who had CAD alone was 53.05 ± 9.64 years, while in the group who had multivascular morbidity mean age was 59 ± 5.75 years. This difference in age was statistically significant.

4) Mean duration of diabetes among patients with CAD alone was 3.22 ± 4.3 years. While mean duration of diabetes in patients with multivascular involvement was 6.45 ± 5.25 years. This difference was statistically significant.

5) Mean fasting blood sugar was 141.13 ± 26.76 mg/dL and 160.47 ± 42.5 mg/dL in patients with CAD alone and those with multivascular morbidity respectively. This difference was statistically significant. Mean post-meal

sugar in patients with CAD alone and patients with multivascular morbidity was 216.49 ± 58.84 mg/dL and 241.92 ± 79.89 mg/dL respectively. The difference was found to be statistically insignificant.

6) Mean HDL in patients with CAD alone was 39.92 ± 4.71 mg/dL, while in those with multivascular morbidity was 36.98 ± 4.62 mg/dL. The difference was statistically significant.

7) On multiple logistic regression analysis, multivascular morbidity was significantly associated with age of the patient and duration of diabetes after adjustment for other risk factors like hypertension, dyslipidaemia and fasting blood sugar.

Limitation of the Study

Present study has not taken into consideration the long-term diabetes control in the form of glycated haemoglobin (HbA1C). Also, aortic stiffness (measured non-invasively by brachial-ankle pulse wave velocity) and renal artery involvement by atherosclerosis were not taken into consideration in the present study.

Abbreviations

ABI   - Ankle Brachial Index.
ba PWV - Brachial Ankle Pulse Wave Velocity.
CA   - Carotid Atherosclerosis.
CABG   - Coronary Artery Bypass Grafting.
CAD   - Coronary Artery Disease.
CAG   - Coronary Angiography.
CCA   - Common Carotid Artery.
DM   - Diabetes Mellitus.
ECA   - External Carotid Artery.
ECG   - Electrocardiography.
FBS   - Fasting Blood Sugar.
HbA1C   - Glycated Haemoglobin.
HDL   - High Density Lipoprotein.
HT   - Hypertension.
ICA   - Internal Carotid Artery.
IMT   - Intima Media Thickness.
KFT   - Kidney Function Test.
LDL   - Low Density Lipoprotein.
MI   - Myocardial Infarction.
PCI   - Percutaneous Coronary Intervention.
PVD   - Peripheral Arterial Disease.
SD   - Standard Deviation.
TG   - Triglyceride.
TIA   - Transient Ischaemic Attack.
TMT   - Treadmill Test.
VLDL   - Very Low Density Lipoprotein.

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