

Research Article

Pattern of macrovascular disease phenotypes amongst newly diagnosed type 2 diabetic patients in a rural institute in Uttar Pradesh, India

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ABSTRACT

Background: The objective of current study was to determine the proportion of Macrovascular Disease (MVD) phenotypes amongst newly diagnosed type 2 diabetic patients in our institute by dividing the cases into sub-groups according to the MVD sites involved (NMVD - no macrovascular disease; NSCS - non-significant carotid stenosis; CBVD - cerebrovascular disease; CAD - coronary artery disease; PAD - peripheral artery disease; PVD - polyvascular disease) and studying the anthropometric, clinical and laboratory parameters in each group.

Methods: The study included a cohort of 136 newly diagnosed patients with T2 DM. Demographic, clinical and laboratory parameters were included in analyses. Standardized procedures were used to assess the risk factors of associated metabolic syndrome (MetS).

Results: The proportion of patients with MVD was 27.94% amongst the participants in the study. The majority of patients with MVD were in the CAD group (15.44%). Age, male sex and smoking history were independent risk factors in the CAD and PAD groups ($P < 0.01$). A low HDL-C value was an independent risk factor in the CAD and PVD group ($P = 0.03$). Very high frequencies of MetS were observed in the PAD and PVD groups (90% and 91.7% respectively). Prevalence of PVD was three times more common in males as compared to that in females. All patients with PAD had associated CAD also.

Conclusion: This study projects a high proportion of MVD amongst newly diagnosed Type 2 diabetics in rural sub-population in Uttar Pradesh. High rates of mortality and morbidity in these patients due to macroangiopathy warrant early screening of MVD to ensure timely preventive and therapeutic measures.

Keywords: Type 2 diabetes mellitus, Macrovascular disease, Cardiovascular risk factors, Metabolic syndrome, Carotid intima-media thickness, Ankle-brachial Index, Macroangiopathy

INTRODUCTION

Macrovascular Disease (MVD) due to widespread and rapidly progressive atherosclerosis is one of the most established complications in patients with type 2 diabetes mellitus (T2 DM). Macrovascular complications, including stroke, Myocardial Infarction (MI) and Peripheral Arterial Disease (PAD) are the leading cause of morbidity and mortality amongst patients with T2 DM

and Cardiovascular Disease (CVD) risk is 2-8 fold higher in the diabetic population than it is in the non-diabetic individuals of similar age, sex and ethnicity.^{1,2} Furthermore, MVD is the largest contributor to the direct and indirect costs of diabetes.³ Though, there are several studies on pattern of macrovascular disease in patients with T2 DM in urban areas, to the best of our knowledge, there is no study conducted to analyze the quantum, pattern and proportion of MVD sub-group phenotypes in

patients with newly diagnosed T2 DM in the rural sub-population of Uttar Pradesh in India.

Objective

The objective of our study was to determine the proportion of macrovascular disease phenotypes in patients with newly diagnosed T2 DM in the rural sub-population of Uttar Pradesh in India by dividing cases into sub-groups according to the vascular sites involved (NMVD - no MVD; NSCS - non-significant carotid stenosis; CBVD - cerebrovascular disease; CAD - coronary artery disease; PAD - peripheral artery disease; PVD - polyvascular disease). We also studied differences among these sub-groups in their anthropometric, clinical and laboratory characteristics, as well as their metabolic syndrome prevalence and severity.

METHODS

Subjects

This prospective, cross-sectional and hospital based observational study was carried out in the department of internal medicine, Uttar Pradesh rural institute of medical sciences and research, Saifai, Etawah, UP, India for a period of one year starting from first of July, 2011. The study included a cohort of 136 patients with newly diagnosed T2 DM, who attended diabetes OPD, General OPD and patients admitted in medical wards. All of the patients included in the study fulfilled the inclusion criteria of patients with newly diagnosed T2 DM residing in rural Uttar Pradesh. Newly diagnosed type 2 diabetics were defined as those patients with T2 DM who were presented to us within six months of their diagnosis of diabetes. The criteria used for the diagnosis of diabetes were fasting plasma glucose (FPG) ≥ 126 mg/dl; or 2 hour post-prandial/ OGTT plasma glucose ≥ 200 mg/dl or classic symptoms of hyperglycemia and random plasma glucose ≥ 200 mg/dl or glycosylated hemoglobin (HbA_{1c}) $\geq 6.5\%$.⁴ Patients with T2 DM were diagnosed on clinical grounds based on age of presentation, insulin requirements and after ruling out causes of secondary diabetes. The exclusion criteria were as follows: patients with type 1 DM, patients with T2 DM with duration of illness more than six months, patients with acute illness, patients on glucocorticoid therapy and patients with advanced liver and kidney diseases. Local ethics committee approved the study.

Clinical and laboratory measurements

- a) Detailed history with emphasis on atherosclerotic vascular events as documented by previous medical records.
- b) Thorough general physical examination; thorough cardiovascular, central nervous system and peripheral vascular system examination

c) Anthropometric measurements

1. Body weight: in kg measured in light clothing without shoe.
2. Height in meters measured to the nearest half centimeter.
3. Body Mass Index (BMI): calculated as weight in kg divided by square of height in meters. For BMI, a cut-off value of 23 kg/sq.m was adopted for the study as per the WHO standards for Asian Indians.
4. Waist Circumference (WC): measured in the standing position at the level of umbilicus to the nearest of half centimeter. Cut-off values for WC were taken 90 cms and 80 cms for men and women respectively.
5. Blood Pressure (BP): measured using standard mercury sphygmomanometer. Three BP readings were obtained at one minute interval and readings were averaged for use in the analysis.

d) Laboratory measurements

1. Routine investigations including FPG, 2 hour post prandial plasma glucose; KFT, LFT, electrolytes, urinalysis etc. were carried out in all patients.
2. The FPG, and lipid profile samples were obtained after 12 hours of overnight fasting using the Olympus All-400 auto analyzer. The value of LDL-C was calculated using Freidewalds formula except when the serum triglyceride concentration was more than 400 mg/dl. Dyslipidemia was defined based on NCEP-ATP 3 guidelines and normal cut-off values were taken as total cholesterol less than 200 mg/dl; LDL-C less than 100 mg/dl and triglycerides less than 150 mg/dl; and values outside these limits were considered abnormal. Values of HDL-C less than 40 mg/dl were considered low.
3. Glycosylated hemoglobin (HbA_{1c}) was measured by High Performance Liquid Chromatography (HPLC) and values equal to or more than 6.5% was considered diagnostic of diabetes.
4. The Metabolic syndrome (MetS) was diagnosed using NCEP-ATP 3 criteria when three or more of the following were present: central obesity: WC ≥ 90 cm (M), ≥ 80 cm (F); triglycerides ≥ 150 mg/dl or specific medication; HDL-C < 40 mg/dl and < 50 mg/dl respectively in males and females or specific medication; BP $\geq 130/85$ mmHg or specific medication and FPG ≥ 100 mg/dl or specific medication or previously diagnosed T2 DM.⁵
5. Carotid Intima-Media Thickness (CIMT): CIMT, a well-standardized, effective surrogate marker for

assessing cardiovascular risk and a well-accepted parameter of subclinical and clinical atherosclerotic vascular disease; was measured by B mode ultrasound having an electric transducer with a mid-frequency of 7.5 MHz. The final CIMT considered was the average of the CIMT values at the twelve sites of both the carotids examined. An upper limit of 0.9 mm was chosen for the present study based on epidemiological data currently available.

6. Ankle-brachial Index (ABI): The Ankle-brachial Index (ABI), a surrogate marker of atherosclerosis, is a simple, non-invasive, reasonably accurate and reproducible test for the detection of PAD, to determine disease severity and to predict future cardiovascular events and all-cause mortality. The ABI was calculated as the ratio of the ankle systolic pressure as the numerator, over the higher brachial systolic pressure in the denominator. The ABI was calculated in each leg separately, and the lower of the two values was taken as the result for the patient to be used in the analyses.

e) *Macrovascular disease evaluation and definition:*

Relevant laboratory studies such as standardized ECG, 2D ECHO, provocative tests for cardiac ischemia-TMT or stress ECHO, Ankle-Brachial Index (ABI) and Duplex ultrasonography of the carotid and lower limb vessels were carried out in all of the patients. The subjects who were diagnosed with MVD; were divided into following six sub-groups:

1. Non-Significant Carotid Stenosis (NSCS) diagnosis: Asymptomatic patients with 50-69% diameter of carotid stenosis in any section of carotid system as detected by Duplex Ultrasonography (DUS) were diagnosed with NSCS.
2. Cerebrovascular Disease (CBVD) diagnosis: Patients with a history of Transient Ischemic Attack (TIA); previous stroke as confirmed by CT/MRI brain scans or previous significant or symptomatic carotid stenosis and patients who had previously been undergone surgical or endoluminal interventions were diagnosed with CBVD. However, asymptomatic patients with hemodynamically significant stenosis ($\geq 70\%$ diameter stenosis in any section as detected by DUS and confirmed with CT angiography) were also included in this group.
3. Coronary artery disease(CAD) diagnosis: We included in this group all of the patients with previously documented Acute Coronary Syndromes (ACS: STEMI, NSTEMI and USA) diagnosis; patients with ischemic heart disease with Chronic Stable Angina (CSA); and asymptomatic patients who were positive for provocative myocardial ischemia on stress evaluation (TMT or stress ECHO). After initial work-up, all of these patients

were referred to higher centres for coronary angiography.

4. Peripheral Artery Disease (PAD) diagnosis: Patients who had previously been undergone endoluminal or surgical revascularization procedures, had previous amputation or had been diagnosed with ischemic ulcers were given the diagnosis of PAD. All of the symptomatic patients (Fontaine's classification stage 2-4) who were confirmed with ABI and DUS were diagnosed with PAD. Asymptomatic patients with ABI < 0.9 who had significant stenosis or occlusion as determined by DUS and confirmed with peripheral CT angiography were also included in the PAD group. One patient with critical limb ischemia was referred to higher centre for revascularization procedure.
5. Polyvascular Disease (PVD) diagnosis: When two or more of the above mentioned conditions were present at the same time, the patients were diagnosed with PVD.
6. No Macrovascular Disease (NMVD): Patients who did not meet the criteria mentioned above were not considered to have MVD.

Statistical analysis

The data were tested for normalcy using Kolmogorov-Smirnov test, which indicated a non-Gaussian distribution for all continuous variables; therefore, the results were reported as a median value and an interquartile range (IQR, 25th-75th quartiles). Univariate analysis was performed with the non-parametric Kruskal-Wallis test and Dunn's multiple comparison post-hoc test to compare each of the continuous variable of interest among the macrovascular sub-groups. The qualitative variable data were expressed as frequencies; and the groups were compared using the chi-square test. Multivariate logistic regression analysis was used to determine whether traditional cardiovascular risk factors (age, sex, smoking status, WC, SBP, DBP, LDL-C, HDL-C, TG levels, HbA1C, FPG, 2HrPPG and presence of MetS) were associated with prevalent CVD (dependent variable, MVD; reference group, NMVD); and the results were expressed as Odds Ratio (ORs) \pm 95% CI. The ORs were calculated using exponential logistic regression coefficients. A P value of less than 0.05 was considered to be statistically significant.

RESULTS

Clinical and biochemical patient characteristics are presented in Table 1. Of total patient population (n=136; M=72, F=64); 98 patients (72.06%) had no evidence of MVD and remaining 38 patients (27.94%) had MVD. (Figure1, panel A). There were 6 patients (4.41%) with MVD who were classified as NSCS; 8 patients (5.88%) with MVD classified as CBVD; 21 patients (15.44%)

with MVD classified as CAD; 3 patients (2.21%) with MVD classified as PAD and 15 patients (11.02%) with

MVD classified as PVD (Figure 1, panel B) (Table 2).

Table 1: Clinical and biochemical patient characteristics.

Variable	All	NMVD (1)	NSCS (2)	CBVD (3)	CAD (4)	PAD (5)	PVD (6)	P diff. among the groups
Patients (%)	136	98 (72.06%)	6 (4.41%)	8 (5.88%)	21 (15.44%)	3 (2.21%)	15 (11.02%)	-
Age (YY)	67 (58-75)	63 (55-72)	66 (59-71)	73 (66-79)	65 (55-75)	72 (65-76)	68 (62-74)	1≠3,5,6***
Sex (%M)	55%	45.3%	40.2%	49.4%	58.6%	64%	61.2%	***
Wt. (Kg)	67 (48-86)	61 (52-70)	64 (58-70)	68 (60-76)	66 (58-74)	65 (56-74)	68 (60-76)	1≠3,6**
BMI (Kg/M ₂)	25.6 (20.9-30.3)	24.1 (19.7-28.5)	25.1 (19.9-30.3)	26 (20.1-31.9)	27.6 (21.2-34)	21.2 (18.1-24.3)	21.4 (18.2-24.6)	1≠6**
WC (Cm)	96 (84-108)	92 (76-108)	98 (84-112)	102 (88-116)	104 (86-122)	102 (84-120)	100 (90-110)	ns
%Smoking H/O	42.8%	39.2%	38.1%	39.4%	40.2%	59.4%	49.2%	***
SBP (mmHg)	130 (120-140)	130 (120-140)	130 (120-140)	145 (130-160)	142 (127-157)	145 (130-160)	140 (130-150)	ns
DBP (mmHg)	80 (70-90)	80 (70-90)	80 (70-90)	84 (74-94)	86 (76-96)	82 (72-92)	86 (76-96)	ns
TC(mg/dl)	178 (151-205)	183 (157-212)	201 (175-221)	176 (153-204)	162 (132-193)	179 (156-212)	165 (135-196)	1≠4,6**
HDL-C (mg/dl)	45 (38-55)	47 (39-57)	49 (39-58)	38 (30-46)	36 (28-44)	33 (25-41)	35 (27-43)	1≠4,6***
LDL-C (mg/dl)	102 (77-131)	105 (83-133)	121 (99-144)	101 (76-129)	121 (99-144)	109 (99-119)	106 (90-112)	ns
TG (mg/dl)	209 (140-278)	201 (130-272)	202 (130-274)	218 (152-284)	209 (152-266)	188 (130-246)	208 (140-276)	ns
HbA _{1C} (%)	8.1 (7-9.5)	8.1 (7.1-9.7)	8 (6.9-10.2)	8.2 (6.8-9.5)	8.1 (7.2-9.5)	8.5 (7.6-9.7)	8.4 (7.4-9.4)	ns
FPG (mg/dl)	174 (139-234)	174 (138-230)	177 (148-232)	169 (138-213)	182 (142-222)	177 (140-218)	174 (137-219)	ns
2HPPG (mg/dl)	201 (160-265)	203 (160-270)	219 (174-284)	195 (160-232)	205 (160-270)	200 (167-237)	200 (155-245)	ns
CIMT (mm)	0.91 (0.85-0.92)	0.6 (0.5-0.7)	0.7 (0.6-0.8)	1.1 (0.9-1.2)	1.0 (0.8-1.2)	0.9 (0.8-1.0)	0.88 (0.72-1.04)	1≠3,4,5**
ABI	1.1 (0.9-1.3)	1.1 (0.9-1.3)	1.1 (0.9-1.3)	1.0 (0.9-1.1)	1.0 (0.9-1.1)	0.6 (0.5-0.7)	0.8 (0.6-1.0)	1≠4,5,6**

Data are medians (IQR, 25th-75th quartiles) ns: non-significant; *P <0.05; **P <0.01; ***P <0.001

Univariate analyses

Macrovascular disease, anthropometric and clinical data:

Patients with CBVD, PAD and PVD were older than those patients in the other sub-groups. Patients in the CAD subgroup were similar in age to those patients without complications and to those patients in the NSCS sub- group. Male patients were more numerous in the

CAD, PAD and PVD sub-groups, whereas female patients were more numerous in the other sub-groups. BMI was significantly lower in the PAD and PVD sub-groups compared to that in NMVD, NSCS, CBVD and CAD sub- groups.

Macrovascular disease and metabolic parameters

We found no difference in the metabolic parameters among the six sub-groups. The HbA_{1C} levels, FPG levels,

2 HrPPG levels were comparable among all the sub-groups. All of the data were outside the normal range at this first observation at our centre.

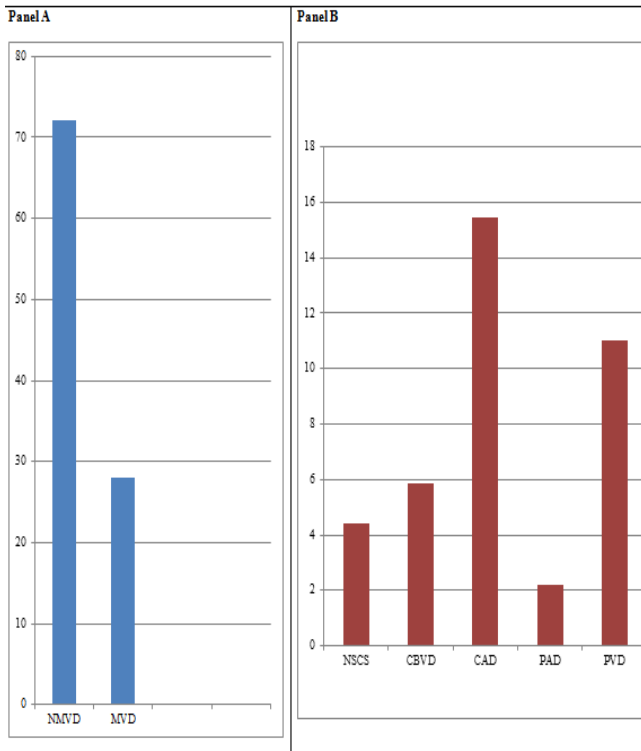


Figure 1: Panel A: MVD in our population, Panel B: MVD sub-groups in the patient population.

Table 2: Proportion of MVD sub-groups among 136 newly diagnosed patients with T2 DM.

Categories by organ system	Number of individuals	Percentage (%)
No MVD	98	72.06
MVD	38	27.94
1) NSCS	6	4.41
2) CBVD	8	5.88
3) CAD	21	15.44
a) Chr. Stable angina	9	6.62
b) ACS (STEMI/NSTEMI/USA)	8	5.88
c) Post PCI/CABG	2	1.47
d) Ischemic cardiomyopathy	2	1.47
4) PAD	3	2.21
5) PVD	15	11.02

Macrovascular disease and lipid profile

HDL-C was significantly lower in the CAD, CBVD and PVD sub-groups compared to that in the NMVD and NSCS sub-groups. No significant differences were observed in the total cholesterol, LDL-C and TG values among the sub-groups.

Macrovascular disease and metabolic syndrome

MetS prevalence was significantly greater in the patients who had macrovascular disease than in those patients who did not have macrovascular complications. The highest prevalence of MetS was recorded in the PAD (90%) and PVD (91.7%) sub-groups. The simultaneous presence of 3 or 4 diagnostic MetS criteria (indicating of severity of MetS) was more frequent in the CAD sub-group (56%; Figure 2).

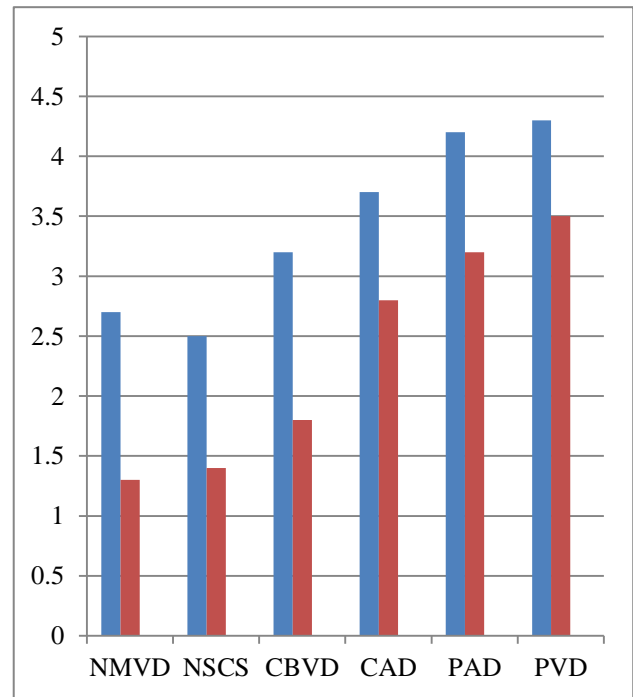


Figure 2: Proportion of patients with Metabolic Syndrome (blue columns) and severity (red columns).

The data are frequencies. CBVD, CAD, PAD and PVD sub-group data are statistically significant at P <0.001 from chi-square test.

Multivariate analysis

Multiple logistic regression analysis was used to determine whether traditional cardiovascular risk factors (age, sex, smoking status, WC, SBP, DBP, LDL-C levels, HDL-C levels, TG levels, HbA1C levels, FPG levels and MetS risk factors) were associated with prevalent CVD (dependent variable, MVD; reference group, NMVD), and data were expressed as Odd's ratio (Table 3). In this analysis, in all of the MVD sub-groups except NSCS, age was significantly associated with MVD. Male sex was significantly associated with the PAD and PVD sub-groups. Reduced HDL-C was independently associated with CAD and PVD sub-groups. MetS diagnosis was independently associated with the PVD and PAD sub-groups. In the logistic regression model, the inclusion of logarithmically transformed values of HDL-C, LDL-C and triglycerides did not change the results.

Table 3: Multivariate logistic regression analysis.

Variable	NSCS			CBVD			CAD			PAD			PVD		
	OR	95%CI	P	OR	95%CI	P	OR	95%CI	P	OR	95%CI	P	OR	95%CI	P
Gender (male)	1.03	0.54-1.96	0.94	1.35	0.70-2.62	0.37	1.53	0.85-2.74	0.16	2.90	1.37-6.12	0.005	2.39	1.53-3.73	0.001
Age	1.03	0.97-1.01	0.09	1.10	1.06-1.13	0.0001	1.02	0.99-1.04	0.28	1.90	1.05-1.14	0.001	1.11	1.08-1.13	0.0001
WC	0.99	1.0-1.06	0.36	0.97	0.95-0.99	0.01	0.99	0.98-1.00	0.45	0.98	0.96-1.00	0.07	0.99	0.97-1.00	0.04
Smoking h/o (yrs.)	0.98	0.52-6.38	0.35	1.44	0.35-5.90	0.62	0.97	0.26-1-90	0.49	2.02	0.63-6.43	0.24	0.85	0.42-1.73	0.45
SBP	1.81	0.99-1.04	0.18	1.01	0.98-1.03	0.46	1.05	0.94-0.99	0.007	1.03	1.01-1.06	0.01	0.99	0.98-1.02	0.73
DBP	1.02	0.94-1.02	0.41	0.97	0.95-1.04	0.84	0.97	1.01-1.10	0.009	0.95	0.91-0.99	0.03	1.01	0.98-1.04	0.75
HDL-C	0.98	0.97-1.02	0.66	0.99	0.97-1.02	0.74	0.99	0.95-0.99	0.02	0.84	0.95-1.00	0.06	0.98	0.97-0.99	0.19
LDL-C	0.96	0.99-1.01	0.16	1.00	0.99-1.01	0.41	1.01	0.98-0.99	0.03	0.77	0.91-1.05	0.66	1.00	0.99-1.02	0.03
TG	1.00	0.99-1.03	0.45	0.99	0.87-1.34	0.18	1.00	0.99-1.02	0.07	1.00	0.99-1.03	0.65	1.00	0.84-1.13	0.09
HbA _{1c}	0.94	0.76-1.15	0.53	1.08	0.99-1.00	0.48	0.93	0.76-1.03	0.45	1.00	0.60-1.03	0.006	3.42	0.99-1.04	0.48
FPG	1.00	0.99-1.02	0.26	0.99	0.87-1.03	0.35	1.03	0.99-1.01	0.33	0.78	1.00-1.02	0.09	0.98	1.01-5.29	0.75
MetS	1.29	0.47-3.57	0.62	1.33	0.43-4.12	0.62	1.10	0.37-3.27	0.86	1.81	0.34-9.37	0.51	1.00	0.97-1.07	0.95
CIMT	0.91	0.8-1.1	0.54	1.00	0.8-1.20	0.52	0.91	0.80-1.10	0.71	1.81	0.7-0.9	0.49	2.30	0.7-3.4	0.03

Relationship among selected variables and the macrovascular groups. (Dependent variable, macrovascular sub-groups; reference group, NMVD). Values in bold are statistically significant.

DISCUSSION

The first goal of our study was to determine the proportion of macrovascular disease in patients with newly diagnosed T2 DM in the rural sub-population of Uttar Pradesh in India. Our study demonstrated that 27.94% of our patient population had macrovascular disease at the time of diagnosis of T2 DM. It is well known that CVD prevalence, incidence, morbidity and mortality are strikingly greater in the diabetic than in the non-diabetic population. According to the WHO, CVD prevalence in the diabetic population ranges from 26%-36%.⁶ Though, the prevalence of macrovascular disease in our population (27.94%) was comparable to the WHO and other western data, it was significantly higher than that demonstrated by other studies conducted in India.⁷⁻¹¹ The significantly higher prevalence of macrovascular complications in our patient population is likely linked to the patient characteristics (average age, lack of awareness etc.) and due to our inclusion of NSCS patient sub-group to the MVD group.

Advanced atherosclerotic vascular changes are often preceded by impairment of endothelium dependent vasodilatation, vascular smooth muscle dysfunction and increased arterial stiffness. Today, all of these factors are recognized as predictors of vascular dysfunction in patients with T2 DM. Atherosclerotic disease usually causes systemic involvement which is more frequent in diabetic population. Moreover, atherosclerosis in diabetic patients is different from that in non-diabetic subjects because both pathological studies and angiographic reports in individuals with CVD have shown that diabetic patients have more blood vessels involved, with a more diffuse atherosclerotic lesion distribution.¹²

To the best of our knowledge, no study has been conducted on patients with newly diagnosed T2 DM in rural population of Uttar Pradesh to compare the anthropometric, clinical and laboratory features by stratifying them according to the sub-type of macrovascular disease phenotype. By analyzing anthropometric, clinical and laboratory characteristics of

sub-groups of the MVD patients, we found that patients with PAD and PVD sub-groups were older, were more likely to have been smokers, had lower weight, BMI and WC than did the patients in the other sub-groups. A multivariate analysis demonstrated that age, male sex and smoking status were the most important independent PAD and PVD risk factors. It is noteworthy that the same characteristics were not found to be the independent risk factors in the CAD sub-group and that the average patient age in this patient sub-group was comparable to that of the population without macrovascular complications. The question arises whether a genetically determined predisposition alone may explain the early onset of cardiac involvement in the patients in the CAD sub-group. In recent years, many genetic risk factors for both diabetes and CAD have been discovered through genome-wide association studies. Genetic aspects of diabetes and MVD may share mechanisms, leading to a common effector hypothesis. However, only a few genetic risk factors could be identified that modulate the risk for both the conditions. Polymorphism in the TCF7L2 and CDKN2A/B genes may be of great importance for CAD development because these genes modulate both conditions and are not necessarily related to hyperinsulinemia or hyperglycemia.^{13,14}

By analyzing glyco-metabolic parameters, (FPG, 2HPPG, HbA_{1c}) we found no differences among the six sub-groups. Despite a clear association between diabetes and atherosclerotic vascular disease, the underlying mechanism responsible for the two diseases is not fully understood. The relative importance of the “non-glycemic” risk factors and hyperglycemia “per se” has always been debated.¹⁵ Results on the causal relationship between hyperglycemia and macroangiopathy have been contradictory. Plenty of evidence suggests a significant relationship between HbA_{1c} levels and post prandial hyperglycemia and adverse outcomes especially in overweight and obese patients.^{16,17} However, recently three major studies ACCORD, ADVANCE and VADT¹⁸ evaluated the impact of attaining euglycemia (ACCORD) or near-euglycemia (ADVANCE and VADT) in patients with long lasting diabetes and high cardiovascular risk. None of the studies, either individually or on pooled analysis, demonstrated any reduction in the all-cause or cardiovascular mortality; although a meta-analysis revealed a 15%-17% reduction in the incidence of non-fatal myocardial infarction in those patients exposed to tight glucose control.¹⁸ A higher mortality was observed in the intense glucose control arm of ACCORD, leading to the premature termination of the glucose-lowering component of this study. The weak association between glycemic control and macrovascular disease observed in the UKPDS¹⁹ study has been confirmed and amplified by these recent intervention studies. Accordingly, our data show that HbA_{1c}, 2HrPPG and FPG were similar in the each sub-group considered. However, the relationship between hyperglycemia and macrovascular complications is made even more complex by the potential role of epigenetic mechanisms, as the metabolic memory, by

which a prior exposure to hyperglycemia predisposes diabetic patients to the continuing development of the vascular diseases despite a subsequent good glycemic control.

By analyzing the lipid profile, we found a clear difference in HDL-C among the sub-groups, which was lower in the CAD, PAD and PVD sub-groups. These data are in accordance with other scientific evidence that supports the importance of this macroangiopathy-associated risk-factor.²⁰ In a multivariate analysis, we also confirmed that reduced HDL-C values are independent CAD and PVD risk factors. (The association was borderline significant for the CBVD sub-group.)

Many reports have suggested that metabolic syndrome may precede or predict vascular disease. It has been reported that insulin resistance and MetS also increase the risk of new cardiovascular events in patients without known diabetes but with manifest arterial disease.²¹ In T2 DM, MetS is highly prevalent and often precedes hyperglycemia onset. Furthermore, insulin resistance and MetS predict atherosclerosis in patients with T2 DM. Our findings support the clinical relevance of MetS components detection, which may be simple, quick tool to stratify diabetic patients according to the expected macrovascular complication severity (as a polydistrectual disease).

Measurement of Carotid Intima-Media Thickness (CIMT) with B-mode ultrasound is a well-standardized, effective, non-invasive, sensitive and reproducible surrogate marker for identifying and quantifying sub-clinical and clinical atherosclerotic vascular disease and for evaluating CVD risk.²² Moreover, CIMT is a strong predictor of future cardiovascular events and is associated with conventional markers of CV risk such as age, hypertension, dyslipidemia etc.²³ A CIMT of less than 0.55 mm have been found to be an excellent marker of the absence of macrovascular disease especially CAD. In our study, the mean value of CIMT was 0.91 mm with females having a relatively lower value as compared to that in males; possibly due to the protective effects of female hormones and/ or male gender being at higher risk of atherosclerosis. In our study, we did not observed any significant correlation between age of the patients and values of CIMT. The CIMT was found to be higher among patients with central obesity and other components of MetS. However, there was no definite association observed between BMI and CIMT. This observation emphasizes the emerging concept that the body composition rather than the size may be more relevant risk for CVD. Our study also demonstrated that increased CIMT values are strong and independent predictors of CAD, PAD and PVD sub-groups.

The Ankle-Brachial Index (ABI) is a surrogate marker of atherosclerotic vascular disease and recent studies indicate its utility as a predictor of future cardiovascular events and all-cause mortality.^{24,25} Based on ABI defining

criteria, the prevalence of PAD was found in 2.21% of the patient population which is low from the figure published in the western literature. Though ABI values were higher among males and smokers as compared to those in females and non-smokers, the values did not achieve statistical significance ($P = 0.06$). Besides PAD, ABI was a strong and independent predictor of CAD, CBVD and PVD sub-groups.

CONCLUSION

This study projects a high proportion (27.94% of the patient population) of polydistrectual atherosclerotic MVD amongst patients with newly diagnosed T2 DM in rural sub-population in Uttar Pradesh. The characterization of various phenotypes of macroangiopathy among newly diagnosed patients with T2 DM may have a clinical significance for the everyday practitioner. Given the high rates of mortality and morbidity in T2 DM patients due to atherosclerotic macrovascular diseases; every possible step is to be undertaken for early screening of MVD in these patients to ensure timely preventive and therapeutic measures.

Abbreviations

ABI: Ankle-brachial index; ACS: Acute coronary syndrome; BMI: Body mass index; CIMT: Carotid intima-media thickness; CAD: Coronary artery disease; CBVD: Cerebrovascular disease; CT: Computed tomography; CTA: Computed tomography angiography; CVD: Cardiovascular disease; DBP: Diastolic blood pressure; DUS: Duplex ultrasonography; FPG: Fasting plasma glucose; MVD: Macrovascular disease; MetS: Metabolic syndrome; NMVD: No macrovascular disease; NSCS: Non-significant carotid stenosis; PAD: Peripheral artery diseases; PTA: Percutaneous transluminal angioplasty; PVD: Polyvascular disease; SBP: Systolic blood pressure; T2DM: Type 2 diabetes mellitus; TIA: Transient ischaemic attack; WC: Waist circumference.

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