

## ORIGINAL ARTICLE

# Frequency of Macrovascular Complications in Patients of Newly Diagnosed Type 2 Diabetes Mellitus and its correlation with Major Cardiovascular Risk Factors; A Hospital Based Study

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## Abstract

**Objective:** Frequency of macrovascular complications in newly diagnosed patients of type 2 diabetes mellitus and its correlation with major cardiovascular risk factors; A Hospital Based Study.

**Methods:** All consecutive newly diagnosed type 2 diabetics were enrolled and evaluated for the presence of cardiovascular risk factors and macro vascular complications i.e. Coronary Artery disease (CAD), Cerebrovascular Disease (CVD) and peripheral vascular disease (PVD).

**Results:** 105 newly diagnosed subjects with diabetes with a mean age of  $56.55 \pm 7.43$  years were enrolled in the study amongst them 53 were male and 52 were females. The mean plasma glucose of these patients was  $178.40 \pm 52.05$  mg%, out of 105 patients enrolled in the study 20 (19.05%) of the patients had macro vascular complications at the time of diagnosis of type 2 diabetes.

**Conclusion:** Type 2 diabetes mellitus can present with or without symptoms and with chronic vascular complications at the time of diagnosis, opportunistic screening for diabetes should be done in high risk patients along with screening for the vascular complications.

## Introduction

Type 2 diabetes (ranging from predominantly insulin resistance with relative insulin deficiency to predominantly an insulin secretory defect with insulin resistance) accounts for 90-95% of those with diabetes.<sup>1</sup> IDF estimates (2013), 592 million (8.3%) of adults suffered from diabetes worldwide and is set to rise beyond 592 million in less than next 25 years. In India 65.1 million (8.7%) people have diabetes which is expected to increase by 71% in the year 2035.<sup>2</sup>

Vascular complications due to atherosclerosis are major cause of morbidity and mortality in subjects with type 2 diabetes. Hyperglycemia has direct and indirect effects on human vascular tree (Vascular complications) which is rapid and accelerated. Injurious effects of hyperglycemia designated as macro vascular complication i.e. coronary artery disease (CAD), peripheral arterial disease (PAD), cerebrovascular

disease (CVD) and microvascular complications (retinopathy, neuropathy and nephropathy) are associated with diabetes in numerous studies like Framingham<sup>3</sup> and UKPDS-6 (United Kingdom Prospective diabetes study-6)<sup>4</sup> etc. The mechanism linking hyperglycemia to these pathological changes in micro and macro vasculature is poorly characterized. The functional changes in long standing hyperglycemia leads to endothelial dysfunction, hemodynamic disturbances, hemorrhagic, coagulation abnormalities and increased capillary permeability. Possible unifying mechanism is that the hyperglycemia leads to production of reactive oxygen species in mitochondria which causes induction of DNA damage, reduced NO bioavailability. Activation of protein kinase C, increased AGE

formation leading to endothelial dysfunction; alter extracellular matrix components and formation of growth factor. The causative role of hyperglycemia in the development of macro vascular complication is less conclusive; however the CAD events and mortality are two to four times greater in patients with type 2 diabetes. Dyslipidemia, Hypertension, smoking and obesity play an important role in macro vascular complications. The pathophysiologic changes associated with atherosclerosis in DM are similar to those seen in non-diabetic, but they appear earlier are more extensive and severe. The present study was aimed at studying profile of vascular (macro vascular) complications and carotid intima media thickness (CIMT) in newly diagnosed patients of type 2 diabetes in sub-Himalayan region.

## Material and Methods

The study was carried out in all consecutive newly diagnosed diabetic patients admitted in the department of Medicine and patients attending diabetic clinic of Indira Gandhi medical college Shimla H.P. over a period of one year. A total of 105 newly diagnosed drug naïve patients were included in the study after obtaining informed consent

Diabetes was diagnosed as per ADA 2013 guidelines. The risk factor like hypertension defined as per JNC VIII, dyslipidemia as per NCEP-ATPIII guidelines. Smokers were defined according to US Center for Disease control and prevention definitions. Patients were labeled as obese if they fulfilled Indian consensus Guidelines for Obesity. The vascular complications

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**Table 1: Frequency distribution of presenting symptoms in newly diagnosed type 2 diabetes (n=105)**

Type of presentations	n (%)
Asymptomatic –routine check-up	24 (24.76%)
Asymptomatic-pre-op check-up	15 (14.26%)
ACS/MI	10 (9.52%)
Stroke /TIA	5 (4.76%)
Vascular claudication	3 (2.86%)
Paresthesia's	8 (7.62%)
Visual Disturbances	4 (3.81%)
Swelling Feet	1 (0.95%)
Polyuria / polydipsia / polyphagia / weight loss	19 (18.09%)
Infections	14 (13.33%)

CAD was defined by the presence of any of the following

Documented Acute myocardial Infraction (AMI) based on history of chest pain, EKG changes and elevated levels of markers of myocardial necrosis.

History of CABG / PTCA.

History of chest pain with inducible ischemia on stress.

ECG evidence of silent myocardial infraction identified by Minnesota code 1:1, 1:2.

ECG evidence of LBBB with RWMA on Echocardiography.

Cerebrovascular disease (CVD) was defined as history of Transient Ischemic Attack (TIA) or Focal deficit or evidence of Stroke on Computerized tomography C.T. scan. Peripheral vascular disease (PVD) was defined as history of intermittent claudication or rest pain associated with any, absent or feeble peripheral pulse or Ankle brachial index (ABI) <0.9. Carotid intima media thickness (CIMT) was measured by B mode scanning of both carotid arteries in each patient by USG 7.5 MHZ linear probe of i-33 Phillips Echo machine. The intimal plus medial thickness was measured as the distance from the leading edge of first echogenic line to the second echogenic line. CIMT of both right and left side was measured and average CIMT was calculated. IMT of > 0.9 was taken as increased intima media thickness (IMT).

#### Statistical analysis

Data was recorded on a Microsoft excel spreadsheet, statistical analysis was performed using Epi Info 2000 (center for diseases control and prevention, Atlanta, GA, USA) and SPSS student version 16.0 (SPSS Inc., Chicago, USA). All discrete variables

**Table 2: Baseline biochemical characteristics in newly diagnosed type 2 diabetes (n=105)**

Variables	Mean value (n=105)	Mean value males (n=52)	Mean value females (n=53)	P value
FBG mg%	178.40±52.05	180.92±52.00	175.92±52.37	.625
PPBG mg%	262.53±55.11	264.40±52.41	260.70±58.07	.732
HbA1c(%)	8.12±1.24	8.22±1.17	8.01±1.30	.390
Total cholesterol	188.79±42.73	190.62±49.14	187.00±35.72	.667
LDL (mg%)	96.09±32.27	96.19±39.47	96.00±23.53	.976
HDL (mg%)	47.18±7.13	46.80±7.55	47.54±6.47	.598
Triglycerides	157.25±60.19	140.02±38.20	173.83±72.12	.004

were expressed as percentages. The differences in distribution of discrete variables were analyzed using chi-square test. Significance of differences in continuous variables were analyzed by students t test and p value of <0.05 was considered as statistically significant.

## Results

This was a prospective observational cross-sectional study conducted in department of Medicine, Indira Gandhi Medical College Shimla Himachal Pradesh from June 2013 to May 2014. 105 consecutive newly diagnosed patients of type 2 diabetes were included in the study.

Baseline characteristics of the study group

#### Age and Sex distribution

Mean age of patients in the study was 56.55±7.3 years (males 54.71±8.32; females 53.86±10.13) with a range of 39-77 years. Out of these 105 patients 53(50.48%) were females and 52 (49.52%) were males. 46 (43.81%) of patients were from rural background in the study.

#### Presenting symptoms

64 (61.95%) of patients out of 105 were symptomatic in the study. Out of these 64 symptomatic patients, 19 (18.09%) patients presented with classical symptoms of polyuria, polydipsia and weight loss and 14 (13.33%) had some infection at the time of diagnosis.

10 (9.52%) patients presented as acute coronary syndrome. 5 (4.76%) patients presented with stroke/TIA and 3 (2.86%) patients had lower limb vascular ischemia. Of the 41 (39.05%) asymptomatic patients, 26 (24.76%) were diagnosed on routine check-up while 15 (14.29%) were detected to have diabetes during pre-operative check-up for fitness for surgery.

Mean fasting plasma glucose in this study was 178.40±52.05mg %

(180.92±52.00 mg % in males and 175.92±52.47 mg% in females). Mean post prandial plasma glucose was 262.54±55.11 mg % (264.40±52.41mg% in males and 260.70±58.07 mg% in females). The mean HbA1c level were 8.12±1.24 % (8.22±1.17% in males and 8.01± 1.30% in females). Majority (81%) of the patients in this study had HbA1c in the range of 6.5 to 9.0% while 19% of the patients had HbA1c more than 9.0% (Table 2). Mean total cholesterol in this study was 188.79± 42.74mg% (190.62±49.14 mg % in males and 187.00±37.72 mg % in females), mean Triglycerides 157.25 ±60.19mg% (males 140.02±38.20 mg%, females 173.83±72.12 mg%, mean HDL cholesterol 47.18±7.13 mg% (46.80±7.55 mg % in males and 47.54±6.74 mg % in females, mean LDL cholesterol was 96.09±32.27 mg% (96.19±39.47 mg% in males and 96.00±23.53mg% in females).

#### Risk factors

In this study 35 (33.33%), males 13 (12.38%) and females 22 (20.95%) patients had family history of diabetes, 39 (37.14%) males 33 (31.43%) and females 6 (5.71%) were smokers (p <0.001), 16 (15.24%) male and 12 (11.43%) females were obese, 27 (25.71%) male and 23 (21.90%) females were hypertensive, 25 (23.81%) females and 16 (15.24%) males had dyslipidemia.

In the study 34 (32.88%) patients had one risk factor, 30 (28.57%) patients had two, 21 (20%) had three and 6 (5.71%) had four and only two patients had all five risk factors i.e. family history of Diabetes, smoking, obesity, hypertension and dyslipidemia. The 20 (19.05%) patients out of 105 patients included in the study had only macro vascular complications while 4 (3.81%) had both micro vascular and macro vascular complications whereas 25 (23.80%) had only micro vascular complications. Amongst macro vascular complication the prevalence of CAD, CVD and PVD was 11.4%, 6.7%, 4.8 % respectively. 37 (35%) of the patients

enrolled had increased CIMT  $\geq 90$  mm. Amongst the total number of patients with increased CIMT (n=37), 6 (16.22%) had CAD whereas 6 (8.82%) of patients with normal CIMT (n=68) had CAD and this correlation was not statistically significant. 7 (18.92%) of the patients in this study with CVD had increased CIMT whereas none of the patient with normal CIMT had CVD in the study ( $p < .0001$ ). 4 (10.81%) patients with PVD had increased CIMT while one patient with normal CIMT had PVD and was statistically significant ( $p=0.032$ ).

### Discussion

The Asian Indian phenotype refers to certain unique clinical and biochemical abnormalities like increased insulin resistance, higher waist circumference despite lower BMI, lower adiponectin and high level of hs CRP making Asians more prone to diabetes and premature coronary artery disease (CAD). Although the classical symptoms of diabetes are present less often in newly diagnosed diabetics and approximately 40% of them may be asymptomatic, one third newly diagnosed patients also have associated vascular (Macro-Micro) complications of diabetes at the time of diagnosis highlighting importance of opportunistic screening of high risk individuals. Patient of the sub continent develop diabetes a decade earlier as compared to their western counterpart as the mean age of patients in this study was  $56.55 \pm 7.3$  years with a range of 39-77 years majority (73.38%) being between 40-60 years. The incidence was similar to other studies like CINDI<sup>5</sup> and study in Nagpur by Saoji<sup>6</sup> showing that majority of patients with type 2 diabetes are in the range of 45-64 years which is in contrast to developed countries in which age at diagnosis of type 2 diabetes is  $>65$  years in majority of patients.<sup>7</sup>

There is clustering of risk factors in subjects diabetes as compared to normal subjects. In this study of newly diagnosed diabetics, 14 (13.44%) patients had no risk factor, 34 (32.38%) patients had at least one risk factor and 57 (54.31%) of patients had 2 or more risk factors. The common risk factors in this study was hypertension (47.61%), followed by dyslipidemia (39.04%) smoking (37.14%), positive family history (33.33%) and obesity in (26.66%) of patients. 49 (46.66%) patients has vascular complications, of these 20 (19.05%) of patients had

macro vascular complications and was similar to the observations made in the landmark UKPDS-6<sup>4</sup> study in which half of the newly diagnosed type 2 diabetics had one or more vascular complication at diagnosis. In a study conducted at Poland,<sup>8</sup> at the time of diagnosis macro vascular complications were present in 12% of patients. Gupta A et al.<sup>9</sup> and a study from Nagpur by Saoji<sup>6</sup> has also reported vascular complications in their newly diagnosed type 2 diabetics as 38.57% and 53.03% respectively, which is similar to present study. The increased prevalence of vascular complications (micro and macro vascular) in almost 50% of patients at the time of diagnosis emphasizes the need for screening of chronic complications at the time of diagnosis and aggressive treatment for glycaemia and cardiovascular risk factors.

Excess mortality in type 2 diabetes is caused by large vessel disease, particularly myocardial infarction and stroke. The pathological changes of atherosclerosis in diabetics are similar to non-diabetic patients, but they occur early in life and are more extensive and severe. The prevalence of coronary artery disease (CAD) in this study was 11.40%. Various studies have shown prevalence of CAD from 4.8-40%. Ruigomez and Rodriguez<sup>10</sup> in UK have reported prevalence of CAD in newly diagnosed type 2 diabetes as 17%. In UKPDS-6<sup>4</sup> study of 2337 newly diagnosed patients, 18 % of the patients had abnormal ECG and 1% had MI. In African continent, the prevalence of CAD in newly diagnosed type 2 diabetics was 4.8% in a study by Namubya et al,<sup>11</sup> and it was 21% in a study from Sri Lanka by Weerasuriya et al.<sup>12</sup> In multicentric CNDI study 6% of newly diagnosed patients had CAD. The prevalence of CAD was 7.61% in newly diagnosed type 2 diabetics in a study by Gupta et al, 10% of patients had CAD in a study by Shukla et al,<sup>13</sup> the variable prevalence of CAD in newly diagnosed type 2 diabetics in different studies is due to non-uniform criteria used in the diagnosis of CAD.

6.7% of the patients enrolled in this study had cerebrovascular diseases (CVD). The prevalence of CVD reported in the studies conducted outside India is between 1-5.6%. A low (1%) prevalence of CVD was seen in UKPDS<sup>4</sup> study of newly diagnosed diabetics.

Prevalence of CVD was 3.22% in a study by Gupta et al<sup>8</sup> from Agra India. Higher prevalence of CVD in this study could be because it being hospital based cross sectional study conducted in tertiary care referral hospital with CT scan facility catering large area of south and central Himachal.

The prevalence of PVD in Hoorn Screening study<sup>14</sup> was 10% and 12% in a study by Ruigomez and Rodriguez. In UKPDS-6 study the prevalence of PVD in newly diagnosed patients with type 2 diabetes was 13%. In India the prevalence of 1-3.5% of PVD has been reported in various studies. The prevalence of 1% was reported by Gupta et al and Shukla et al. respectively. Mohan V et al<sup>15</sup>. have reported prevalence of PVD in newly diagnosed patients 3.5%. The prevalence rate of PVD are higher in western countries as compared to Asia and India and the result of this study i.e. prevalence of 4.80% was comparable to other studies conducted in India.

### Conclusion

Type 2 diabetes mellitus can present with or without symptoms and with chronic vascular complications at the time of diagnosis, opportunistic screening for diabetes should be done in high risk patients along with screening for the vascular complications. Once diagnosed type 2 diabetes should be aggressively treated and all cardiovascular risk factors should be treated to target with periodic monitoring so as to reduce chronic vascular complications. Education of high risk population regarding diabetes related complications must be started to encourage earlier medical consultation.

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