

# Cardiovascular risk factors, micro and macrovascular complications at diagnosis in patients with young onset type 2 diabetes in India: CINDI 2

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## ABSTRACT

**Context:** Type 2 diabetes mellitus (T2DM) in young adults is increasing in India. Data on the prevalence of cardiovascular (CV) risk factors and complications associated with young-onset T2DM (YOD) at the time of diagnosis of diabetes are limited. This data can aid in aggressive diabetes management, CV risk reduction, and prevention of complications. **Aim:** To determine the prevalence of CV risk factors, micro and macrovascular complications in patients with newly diagnosed YOD. To assess the percentage of patients who require statin therapy based on current American Diabetes Association (ADA) guidelines. **Settings and Design:** This was a retrospective cross-sectional study of 1500 patients with newly detected YOD across seven centers from 2013 to 2015. **Designs and Methods:** Patients were evaluated for complications of diabetes and CV risk factors such as body mass index (BMI), hypertension, dyslipidemia, and smoking. **Statistical Analysis:** Measurements have been presented as mean  $\pm$  standard deviation; results on categorical measurements have been presented in percentages. **Results:** The mean age, glycated hemoglobin and BMI were  $34.7 \pm 4.2$  years,  $9.9 \pm 2.4\%$ , and  $26.8 \pm 4.7$  kg/m<sup>2</sup>. Hypertension, dyslipidemia, BMI  $>23$  kg/m<sup>2</sup>, and smoking were presented in 27.6%, 62.4%, 84.2%, and 24%. Diabetic retinopathy, neuropathy, and nephropathy were seen in 5.1%, 13.2%, and 0.9%. Ischemic heart disease, peripheral vascular disease, and stroke were presented in 0.7%, 2%, and 0.1%. As per current guidelines, 95.33% needed statin therapy. **Conclusion:** This study demonstrates that patients with YOD have micro and macrovascular complications at diagnosis. Nearly, every patient required a statin to reduce CV risk. This highlights the importance of screening patients with YOD for CV risk factors and complications of diabetes at the time of diagnosis.

**Key words:** Cardiovascular risk, complications, dyslipidemia, neuropathy, retinopathy, type 2 diabetes, young onset diabetes

## INTRODUCTION

The prevalence of type 2 diabetes mellitus (T2DM) in India is increasing exponentially.<sup>[1]</sup> There has also been

an increase in the number of young adults with T2DM.<sup>[1]</sup> Patients diagnosed to have T2DM under the age of 40 years are designated to have Young onset Diabetes (YOD).<sup>[2]</sup>

In Asian Indians, diagnosis of diabetes occurs at younger ages and lower body mass index (BMI).<sup>[3]</sup> Patients with YOD often have inadequate glycemic control and multiple

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cardiovascular (CV) risk factors. This contributes to an increase in micro and macrovascular complications over time.<sup>[2,4-7]</sup>

The extent of complications and presence of CV risk factors at the time of diagnosis of T2DM in India has been reported in several studies.<sup>[8-11]</sup> Data on patients with YOD are limited. Identification of CV risk factors, complications, and initiation of multifactorial risk reduction is pivotal to diabetes care in this vulnerable population.

The aim of this study was to determine the prevalence of CV risk factors, micro, and macrovascular complications, and assess the need for statin therapy in patients with newly diagnosed YOD in India.

## DESIGNS AND METHODS

This is a retrospective analysis of patients with newly diagnosed YOD attending the outpatient departments of seven specialized diabetes clinics across India between 2013 and 2015. The study population comprised 1500 patients with newly diagnosed YOD. The diagnosis of diabetes was based on the ADA criteria.<sup>[12]</sup> Newly diagnosed diabetes was defined by an arbitrary cut-off point as a known duration of diabetes <3 months. Patients with type 1 diabetes, gestational diabetes mellitus those confirmed or suspected to have latent autoimmune diabetes in adults were excluded. Standard protocols were uniformly followed across all the study centers for patient evaluation and data entry.

Each patient underwent a thorough history and physical examination. History of hypertension, dyslipidemia, smoking, micro and macrovascular complications of diabetes was recorded. Patients were screened for the presence of CV risk factors such as BMI, hypertension, dyslipidemia (low-density lipoprotein [LDL] >100 mg/dl) along with the micro and macrovascular complications of diabetes.

### Definitions

#### Body mass index

Lower BMI cut-offs as per Indian guidelines<sup>[13]</sup> were used to diagnose overweight and obese patients. BMI definitions were as follows:

- <18.5 kg/m<sup>2</sup>: Underweight
- 18.5–22.9 kg/m<sup>2</sup>: Normal BMI
- 23–24.9 kg/m<sup>2</sup>: Overweight
- >25 kg/m<sup>2</sup>: Obese.

#### Hypertension

The blood pressure (BP) was measured in the sitting position, after 15 min of rest in a quiet room. Those with a

BP >140/90 mmHg were diagnosed to have hypertension. This was confirmed at three follow-up BP recordings before the diagnosis was made.<sup>[14]</sup>

#### Dyslipidemia

The diagnosis of dyslipidemia was made in all patients who had an LDL cholesterol >100 mg/dl in a fasting lipid profile.<sup>[15]</sup>

#### Retinopathy

The diagnosis of retinopathy was made by a retinal specialist on a dilated pupil using direct ophthalmoscopy using the early treatment diabetic retinopathy study grading system.<sup>[16]</sup>

#### Nephropathy

The diagnosis of nephropathy was based on the 24 h urine protein estimation or the albumin creatinine ratio (i.e., urinary albumin excretion of  $\geq 300$   $\mu\text{g}/\text{mg}$  of creatinine).<sup>[17]</sup>

#### Neuropathy

The diagnosis of neuropathy was based on symptoms and on clinical examination using a 128 Hz tuning fork, a Semmes Weinstein 10 g monofilament and a biothesiometer. Vibratory perception threshold (VPT) of the great toes was measured in a standardized manner by a single observer and neuropathy was diagnosed if the mean VPT was  $\geq 20$  V.<sup>[18]</sup>

Ischemic heart disease (IHD) was diagnosed based on a treadmill test or coronary angiogram in patients who had an abnormal baseline resting electrocardiogram or a history of physician treated IHD.

Peripheral vascular disease (PVD) was diagnosed clinically based on the history of claudication or the absence of palpable pulsations of the dorsalis pedis and or the posterior tibial artery during the foot examination. This was confirmed by an ankle-brachial index value  $\leq 0.9$  or  $>1.3$  or on Doppler duplex imaging.<sup>[11]</sup>

Cerebrovascular accident (CVA) was diagnosed based on history, clinical examination or history of physician treated CVA/previous computed tomography/magnetic resonance imaging records.

### Statistical analysis

The statistical analysis was carried out using Microsoft Excel and results on continuous measurements have been presented as mean  $\pm$  standard deviation and results on categorical measurements have been presented in percentages (%).

## RESULTS

Of the 1500 patients, 74% were men. The mean age was  $34.68 \pm 4.23$  years and 84% of the patients were aged between

31 and 40 years. The mean glycated hemoglobin (HbA1c) at the time of diagnosis was  $9.86 \pm 2.43\%$  and the mean BMI was  $26.77 \pm 4.7 \text{ kg/m}^2$ . The mean age, HbA1c, BMI in the study population and across each decade are shown in Table 1.

Diabetic neuropathy, retinopathy, and nephropathy were seen in 13.2%, 5.1%, and 0.9% of the patients, respectively. Mild to moderate nonproliferative diabetic retinopathy (NPDR) was present in 4.5% of the patients and 0.5% had severe NPDR. 0.7% had associated maculopathy. None of the patients had proliferative retinopathy, vitreous hemorrhage, or retinal detachment. Macrovascular complications such as IHD, PVD, and CVA were presented in 0.67%, 2%, and 0.1%, respectively. This distribution across each decade is tabulated in Table 2.

Data on the CV risk factors such as smoking, hypertension, dyslipidemia, and BMI  $>23 \text{ kg/m}^2$  across each decade are tabulated in Table 3. The presence of CV risk factors and the application of current guidelines<sup>[15]</sup> called for statin initiation in 95.33% of patients.

The micro and macrovascular complications observed in this study and the prevalence rates in CINDI, CURES, YDRS, and Joint Asia Diabetes Evaluation (JADE) are depicted in Table 4.

**Table 1: Mean age, HbA1c, and BMI**

	Mean age of diagnosis of YOD in years	HbA1c in %	BMI in kg/m <sup>2</sup>
All age groups	34.68±4.23	9.86±2.43	26.77±4.7
<20 years	17.75±2.62	10.87±1.54	22.5±5.21
21-30 years	27.43±1.01	10.14±2.57	26.62±5.32
31-40 years	36.1±2.57	9.81±2.41	26.83±4.57

BMI: Body mass index, YOD: Young-onset T2DM, T2DM: Type 2 diabetes mellitus, HbA1c: Glycated hemoglobin

**Table 2: Micro and macrovascular complications in patients with YOD**

	Neuropathy	Retinopathy	Nephropathy	IHD	PVD	CVA
All age groups (%)	13.2	5.1	0.9	0.7	2	0.1
<20 years	Nil	Nil	Nil	Nil	Nil	Nil
21-30 years (%)	13	3.5	0.9	0.6	1.7	Nil
31-40 years (%)	13.4	5.4	1.0	0.9	2.1	0.2

YOD: Young onset T2DM, T2DM: Type 2 diabetes mellitus, IHD: Ischemic heart disease, PVD: Peripheral vascular disease, CVA: Cerebrovascular accident

**Table 3: CV risk factors across each decade**

	Smoking	Hypertension	Overweight BMI 23-24.9 kg/m <sup>2</sup>	Obesity BMI >25 kg/m <sup>2</sup>	LDL >100 mg/dl	Need for statin based on CV risk
All ages (%)	24.3	27.6	22	61.2	62.4	95.3
<20 years (%)	0	0	0	25	75	75
21-30 years (%)	15.7	13.0	22	56.5	62.6	91.3
31-40 years (%)	26.0	30.4	22	62.3	62.6	96.2

CV: Cerebrovascular, BMI: Body mass index, LDL: Low density lipoprotein

## DISCUSSION

Type 2 diabetes is a major cause for morbidity and death. The global prevalence is on the rise and only one out of every two individuals with diabetes is aware that they have diabetes. The recent Indian study shows that 50% of the population is aware of a condition called diabetes.<sup>[19]</sup> Patients remain undiagnosed as they are asymptomatic for long periods of time. Diagnosis of diabetes is important as it is a major public health problem and adequate control of hyperglycemic and CV risk factors can prevent long-term complications.<sup>[20-23]</sup> Macro and microvascular complications may be present at the time of diagnosis of diabetes due to the insidious nature of the disease. Screening for complications at the time of diagnosis of diabetes is crucial. If present, the progression of these complications can be slowed by aggressive control of hypertension, dyslipidemia, glycemic control, use of angiotensin converting enzyme inhibitors, or angiotensin receptor blockers.<sup>[24-26]</sup>

Asian Indians are known to develop T2DM at a younger age and at a lower BMI.<sup>[3]</sup> Data from CINDI indicates that 46%, i.e., almost half of the patients with type 2 diabetes are diagnosed under the age of 40 years in India.<sup>[8]</sup> Estimates of prevalence across Asia from the JADE Program report that 20%, i.e. nearly one in every five clinic patients have YOD.<sup>[2]</sup>

A younger age of onset implies that patients will need to bear the burden of diabetes for a longer period of time. This in addition to suboptimal control of hyperglycemia and CV risk factors puts them at a greater risk for the development of complications.<sup>[2,4,5]</sup> A recent study from clinic population shows that patients with type 2 diabetes with regular follow-up was associated with significantly lower glycemic burden and lower incidence of retinopathy and nephropathy.<sup>[27]</sup>

**Table 4: Micro and macrovascular complications at the time of diagnosis of type 2 diabetes**

	Present study (%)	CINDI (%)	CURES (%)	YDRS (%)	JADE (%)
Neuropathy	13.2	13.1	-	14.2	11
Retinopathy	5.06	6.01	5.1	26.7	20
Nephropathy	0.93	1.06	0.80	8.4	10
IHD	0.66	6	-	-	5
PVD	2	-	3.5	-	7
CVA	0.13	-	-	-	2

JADE: Joint Asia Diabetes Evaluation, IHD: Ischemic heart disease, PVD: Peripheral vascular disease, CVA: Cerebrovascular accident

The extent of complications and presence of CV risk factors at the time of diagnosis of type 2 Diabetes in India has been reported in several studies such as CURES, YDRS, and CINDI. A subgroup analysis of the complications across each decade in patients with YOD is limited. This prevalence of neuropathy, retinopathy, and nephropathy at the time of diagnosis is similar to the observations in CINDI, YDRS, and CURES.<sup>[8-10,28]</sup> The JADE cohort included all patients with newly diagnosed and known YOD, irrespective of the duration of diabetes. Higher prevalence rates of micro and macrovascular complications have been reported in JADE.<sup>[2]</sup> This only further reiterates the value of screening for complications at the time of diagnosis of diabetes even in young patients, as recognition and aggressive treatment of complications and their risk factors can delay progression of these complications.

This study also demonstrates that CV risk factors are highly prevalent even in young patients with type 2 diabetes. One in every four patients was a smoker, one in three had hypertension, two out of three had dyslipidemia, and four out of five patients had a BMI >23 kg/m<sup>2</sup>. An increase in the CV risk factors was observed as the age advanced across each decade. Dyslipidemia was present even in patients <20 years and the prevalence of all the CV risk factors was much higher beyond the age of 20. The prevalence rates between the third and fourth decade were very similar. The rise in CV risk at an early age highlights the importance of screening for risk factors in all young adults. Similar observations have been reported in JADE.<sup>[2]</sup>

In this study, 62% of patients with YOD had dyslipidemia, i.e., an LDL >100 mg/dl. On applying the current guidelines to clinical practice, the percentage of patients requiring CV risk reduction with statin, increases from 62% to 95.33%. This implies that nearly all patients, even those under the age of 40 years in India, are at a high risk of CV events and require lipid lowering therapy in the form of statins to ameliorate that risk.

This study demonstrates that there is a large group of patients with YOD at risk for CV events. This study underlines the importance of screening all patients with type 2 diabetes for CV risk factors and complications of diabetes at the time of diagnosis.

The Asian Indian phenotype supplemented by an imperfect lifestyle increased the burden of YOD. Identification and optimal treatment of all CV risk factors in addition to glycemic control in this vulnerable population are important in improving the quality and quantity of life.

The strengths of the study lie in the multi centric design and thorough evaluation for diabetes complications. Limitations include male preponderance among the participants that could have resulted in the high proportion of subjects reporting smoking. Furthermore, as the study population comprised patients attending private diabetes clinics, the middle, and upper socioeconomic classes are likely to be overrepresented.

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#### Conflicts of interest

There are no conflicts of interest.

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