Diabetes in India: what is different?

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Purpose of review
The purpose of this study was to review the epidemiology and pathogenesis of diabetes in Asian Indians with a particular focus on 'Asian Indian type 2 diabetes phenotype'.

Recent findings
The prevalence of diabetes is rapidly increasing among Asian Indians, particularly in the past two decades. The diabetes rates in urban India now exceed that seen in Indians migrated to developed nations. Urbanization, changes from traditional healthier diets to high-refined carbohydrate intake, and sedentary lifestyle have contributed to this steep increase in the prevalence of diabetes in India. Type 2 diabetes among Asian Indians is characterized by onset at a younger age, greater abdominal obesity despite relatively lower BMI, greater insulin resistance, and early decline in beta cell function. Asian Indians are also at a higher risk for premature coronary artery disease.

Summary
The clinical profile of type 2 diabetes in Asian Indians differs from Caucasians with higher central obesity, increased inflammatory markers such as high sensitive C-reactive protein, greater insulin resistance, early loss of beta cell function, and a higher risk of coronary artery disease. Mechanistic studies are needed to characterize the pathophysiology of the Asian Indian phenotype.

Keywords
Asian Indian phenotype, Asian Indians, epidemiology, prevalence, south Asian phenotype, south Asians, type 2 diabetes

INTRODUCTION

Diabetes was known to Indian physicians even before 1500 BC [1]. Several ancient texts including the well known Ayurvedic texts (Charak Samhita, 1000 BC and Susruta, 600 BC) gave detailed descriptions of its symptoms and classified diabetes into lean or hereditary and obese or food-induced diabetes, which is not very dissimilar to the present-day classification of diabetes as type 1 (T1D) and type 2 diabetes (T2D) [2].

There is circumstantial evidence from ancient texts and Indian sculptures and paintings depicting large bellied individuals to suggest that obesity and T2D were not uncommon in ancient India [2,3]. Although the exact prevalence of diabetes during the precolonial and colonial periods is not known, it is believed that the repeated invasion by the Arabs and Mughals followed by British colonization leads to impoverishment that might be one of the reasons for the lower prevalence of diabetes during postcolonial independent India [2,3]. Since 1991, socioeconomic conditions in India have dramatically improved, resulting in a rapid increase in the prevalence of T2D. Thus, the increase in prevalence of diabetes in India is one of the major health concerns posing a great economic burden on developing India.

We have reviewed the recent research on epidemiology of diabetes, factors contributed to a rise in diabetes, and characteristics of T2D among Asian Indians.

Epidemiology of diabetes in India

Since the 1960s, a number of studies have estimated the prevalence of T2D in various regions of India. Only multicenter studies are, however, discussed

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KEY POINTS

- The prevalence of T2D in both urban and rural India has increased 10-fold in the last two decades.
- Urbanization, change from traditional healthier diets to those high in refined carbohydrates and fat, and decreased physical activity have contributed to a steep increase in the prevalence of diabetes in India.
- The epidemiology of T2D is changing with the shift of youth to poor urban and rural areas.
- The 'Asian Indian phenotype' is characterized by the onset of T2D at a younger age, greater abdominal obesity despite relatively lower BMI, greater insulin resistance, and early decline in beta cell function.

here. The first national study on the prevalence of T2D in India by the Indian Council of Medical Research (ICMR) was conducted between 1972 and 1975 found the prevalence of T2D in 2.1% of the urban population and 1.5% of the rural population [4]. The 1980s saw a slow, but definite, rise in the diabetes epidemic in both urban and rural India [5,6], and therefore, ICMR conducted a second survey of the prevalence of diabetes. It was reported as 4.1% among urban and 1.5% in rural areas that was almost double compared with the first national survey, especially in urban India [7]. In 2001, a population-based study – National Urban Diabetes Survey – from six large Indian metropolitan cities reported that the age standardized prevalence of diabetes was 12.4% with large variations between different cities [8]. In 2004, the Prevalence of Diabetes in India Study was carried out in 108 centers (49 urban and 59 rural) in different parts of India but excluded metro cities. This study showed a prevalence of diabetes of 5.6% and 2.7% among urban and rural areas, respectively [9]. Another survey, conducted in 2008 in an industrial cohort from five sites in India, showed the prevalence of diabetes in this population was 10.1% [10].

The ICMR-INDIa DIABetes (INDIAB) study is the largest nationwide study on the prevalence of diabetes and is studying all 29 Indian states, two union territories, and the National Capital Region of Delhi in a phased manner. Phase 1 of the ICMR-INDIAB study was carried out in four Indian states, namely, Tamil Nadu (South), Chandigarh (Union Territory, North), Maharashtra (West), and Jharkhand (East). This study reported the prevalence of diabetes (both known and newly diagnosed together) varied from 5 to 13% in different parts of India. Based on these, the overall number of people with diabetes and prediabetes in year 2011 was estimated at 62.4 million and 77.2 million, respectively [11].

Thus, the number of people with diabetes in India has increased from 19 million in 1995 [12] to 32 million in 2000 [13] to 62.4 million in 2011 [11] to 66.8 million in 2014 [14]. The various epidemiological studies conducted over this period of time show at least a 10-fold rise in the prevalence of diabetes in the rural areas is quickly catching up with the urban areas in the prevalence of diabetes in India. The trend of rising prevalence of diabetes over this period of time from various multicenter national studies is shown in Fig. 1.

Rising prevalence of early onset type 2 diabetes among Indians

One of the most worrisome aspects of T2D in Indians is the diabetes onset at a young age. Studies have shown higher prevalence of T2D among young adult Indians [11,15,16]. In a recent clinic-based study from the southern part of India, the prevalence of diabetes in the young (diagnosed $\leq$25 years of age) rose significantly from 0.55% in 1992 to 2.5% in 2009, and this is largely because of the increasing number of T2D, whereas T1D has remained fairly constant [17]. Although it was known that the mean age of onset of T2D in Asian Indians occurs at least a decade or two earlier than in Europeans [17], there is now increasing evidence that it is occurring more frequently among children and adolescents [18].

The problem with the earlier age of onset is that it increases the period of exposure to hyperglycemia, and thus increases the risk of developing long-term diabetic complications by the time they reach early adulthood or midlife. In a study of children and adolescents with a duration of T2D more than 15 years, 81.5% were found to have retinopathy

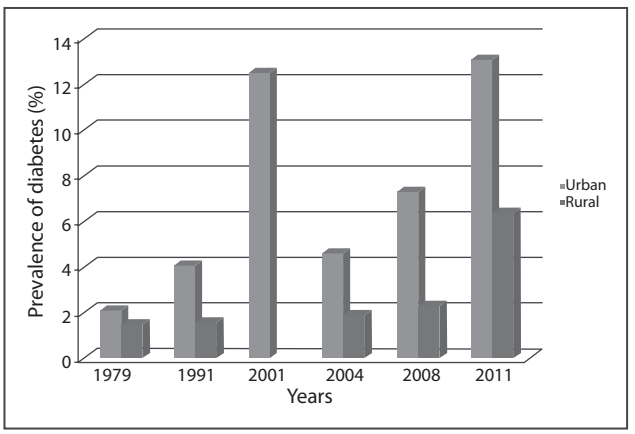

FIGURE 1. The rising trend of diabetes in India in last two decades. Data from [4–11].

and 34.4% to have nephropathy [19], suggesting a higher rate of complications among young T2D. Similarly, a number of studies suggested that early onset T2D may have a more aggressive course than older onset T2D [20,21] or even T1D [22].

Factors contributing to the rise in prevalence of diabetes in India

Socioeconomic conditions are progressively getting better in India during the last two decades, and India has transitioned from lower economic status to middle economic status. The prevalence of most communicable diseases is decreasing, whereas there is a rise in noncommunicable diseases such as diabetes, hypertension, and heart disease. At present, India faces an epidemiologic transition with a 'double burden' of communicable and noncommunicable diseases [23].

The increased availability of high calorie refined and processed foods, introduction of Western diets, and changes from traditionally healthier food habits to 'junk' food higher in fat and sugar has contributed to a rapid rise in obesity and T2D [2,24]. Recent studies have shown a high intake of refined carbohydrates such as white rice and refined wheat is associated with the high prevalence of diabetes in India [25]. Refined cereal intake was also linked to metabolic syndrome [26]. Conversely, the substitution of white rice with brown rice led to decreased blood glucose and insulin levels [27▪]. Physical inactivity has also been shown to be a powerful risk factor for diabetes [28]. Psychosocial factors such as depression may also play a role [29]. Another study from our group showed that five factors – unhealthy diet, obesity, physical inactivity, serum triglycerides, and low HDL cholesterol – explain 80.7% of the population attributable risk for diabetes in this population [30].

Several evidences suggest there is a strong genetic component to T2D among Asian Indians: first, a recent study showed the highest incidence of T2D among Asian Indians compared with any ethnic group except Pima Indians, but the latter are much more obese [31▪]; second, the prevalence of T2D is higher in migrant Indians compared with native populations (e.g., Europeans, Chinese, or Africans) even after an adjustment to age, sex, and BMI [32–35]; third, 36% of Europeans had first-degree relatives with T2D compared with 45% of Asian Indians [36]; fourth, nearly 60% of offspring with two T2D parents had diabetes or impaired glucose tolerance higher than reported in Caucasian populations [37]; and fifth, there is a strong familial aggregation of quantitative traits that are typically associated with T2D [38]. Recent genome-wide association studies have shown that there are some unique genes associated with T2D in Indians [39–41]. As the genes have not changed drastically during the last two decades, whereas the prevalence of diabetes has increased over 10-fold, it is likely that environmental factors are playing a major role in the escalation of the diabetes prevalence in India.

Another hypothesis that explains the increasing prevalence of T2D in India is the 'thrifty genotype hypothesis' [42]. This hypothesis proposed that some genes are selected over previous millennia to allow survival in times of famine by efficiently storing all available energy during times of feast [42]. With the change in socioeconomic status and the continuous availability of calorie dense foods, there is an increase in obesity and T2D in India because of fat accumulation from the role of these genes. This hypothesis also explains the rising prevalence of T2D in American Indians [43].

Studies show that migration from rural areas to urban slums in India led to high rates of obesity, glucose intolerance, and dyslipidemia as a result of a sedentary lifestyle, stress, and higher intake of refined food [44,45].

Low birth weights have been shown to be associated with T2D in several populations [46–48] including Indians [49]. Other factors, such as exposure to industrial chemicals, smoking, sleep deprivation, and/or depression/stress, are a result of modern lifestyles that might also contribute to an increased prevalence of T2D [50–52]. These factors have, however, not been studied well in the Indian population, and more studies on these factors are urgently needed. Various factors linked to rise in the prevalence of diabetes are summarized in Table 1.

Is type 2 diabetes different in India?

Several studies from migrant Indians and among Indians in India have suggested that there is a specific phenotype that makes Indians distinct from Caucasians (or indeed other ethnic groups) and this is referred to as the 'Asian Indian phenotype' [53,54] [Fig. 2].

The Asian Indian phenotype features are as follows.

Onset of diabetes at a young age

In the recent ICMR-INDIAB national diabetes survey, over half of the subjects had an onset of diabetes below 50 years of age [11] that is higher than among people of European origin [55,56].

Table 1. Factors contributing to the rise of diabetes prevalence among Indians

Factors (reference)	
Diet [24–26,27▪]	Higher intake of refined carbohydrates and fats
	Higher intake of 'junk' food
	Increase in calorie consumption
Physical inactivity [28,30]	Urbanization and sedentary life style
	Abdominal obesity
	Hypertension
	Dyslipidemia
Genetics [31▪,38–43]	Higher prevalence compared with other ethnic groups
	Strong familial aggregation
	Unique genes associated with T2D in Indians
	Abdominal obesity, greater insulin resistance
	Thrifty genotype hypothesis
Industrialization [44,45]	Higher stress, sleep deprivation and higher depression among Urban Indians
	Migration from rural to urban area increases the risk for obesity and metabolic syndrome
Low birth weight [46,49]	Studies have shown link between low birth weight and later development of T2D in Indians
Others [50–52]	Industrial chemicals
	Smoking/tobacco
	Alcohol consumption

A study from Canada reported that the median age at diagnosis was lowest among South Asians compared with other ethnic groups including people of other Asian countries [57].

Central (abdominal) obesity

Studies have shown that Asian Indians have larger waist circumferences and abdominal obesity compared with Caucasians despite similar age, BMI, and

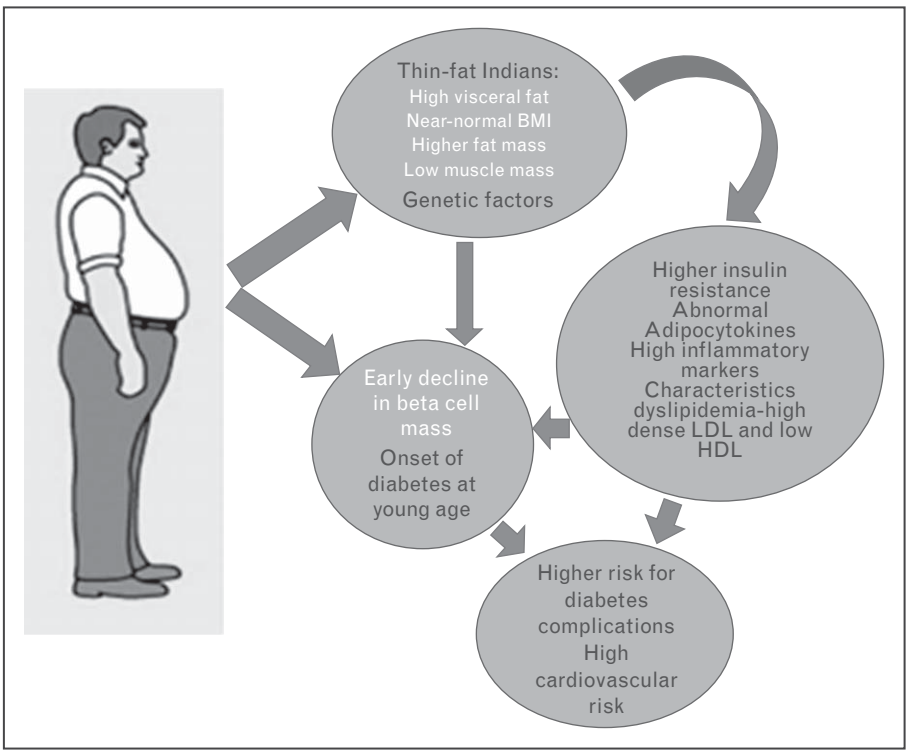

FIGURE 2. Asian Indian phenotype.

total body fat content [58,59]. Such differences in body fat composition are even seen in childhood and adolescence. Indeed, studies have shown that South Asian neonates have significantly more body fat even on the day of birth compared with European children, despite having lower birth weights [60,61].

Greater insulin resistance

Studies have shown that Asian Indians with and without diabetes are more insulin resistant than Caucasians, even at younger ages and comparative levels of BMI and regardless of total body fat [62]. Abdominal obesity might be responsible for insulin resistant and development of diabetes at younger age [63].

Early decline in beta cell function

A study examining both insulin resistant and beta cell function in a group of East Asians, South Asians, Africans, and Caucasians found that despite being matched for lifestyle factors and BMI, the prevalence of insulin resistance in South Asian men was three to four-fold higher than in other ethnic groups [64]. It was also observed that beta cell responsiveness in South Asians was not sufficient to compensate for the degree of insulin resistance [64]. In addition, studies have shown that Asian Indians lose beta cell function very early in the natural history of T2D, even at the stage of prediabetes [65,66]. A prospective study of Asian Indians living in South Africa showed that participants with impaired glucose tolerance exhibited delayed insulin responses indicating early beta cell dysfunction as an underlying pathophysiological abnormality in development of T2D [67].

Asian Indian genotype

Though some T2D genes are common to Asian Indians and European populations [68–70], factors that mediate genetic effects (allele frequencies or polymorphisms) may differ between Asian Indians and Europeans. For example, the fat mass and obesity associated (FTO) gene is associated with T2D in both Europeans and South Asians; however, the association is entirely mediated by BMI in Europeans but not in Asians [69–70]. Moreover, there are unique genes associated with T2D in Indians [39–41,68]. Studies have also found that genetic polymorphisms in various genes are associated with a higher rate of diabetes complications in Indians [71–73]. Since the Indian population is genetically highly diverse, the findings from different studies should be interpreted while taking into account the geographical area and the ethnic group [74].

Increased cardiovascular risk

In an analysis of age-standardized coronary heart disease (CHD) mortality in Canada over a 15-year period, South Asians had the highest CHD mortality compared with individuals of Chinese and European descent [75]. In addition, South Asian men are prone to developing CHD at a younger stage, often before the age of 40 years [76]. The higher risk for CHD events can be attributed to the unique dyslipidemia pattern with low HDL-C, high serum triglycerides, and increased small dense LDL-C, in addition to other factors such as abnormal adipocytokines due to abnormal visceral fat accumulation. The higher levels of serum leptin and C-reactive protein and lower levels of serum adiponectin have also been linked to the metabolic syndrome and high risk for cardiovascular events in Indians [77–79].

Differences in risk of microvascular complications

There are very few population-based studies on complications of diabetes in India. Studies among Asian Indians have shown lower prevalence of diabetic retinopathy [80–83] and higher prevalence of nephropathy [84–87]. Even given the slightly lower prevalence of microvascular complications, the sheer numbers of diabetic patients in India mean that millions are at risk of developing these complications. Shah *et al.* [88] noted that half of the T2D lack the knowledge regarding diabetes and its treatment that might potentially increase the prevalence of complications.

Future directions

Given the enormity of the noncommunicable diseases burden and its economic impact, the Government of India launched the National Programme for Prevention and Control of Diabetes, Cardiovascular Disease, Stroke and Cancer [89]. The objective was to prevent the rise in communicable disease and complications by early diagnosis and treatment.

Despite much progress in characterizing T2D in Indians, many questions remain about why early beta cell dysfunction occurs in Asian Indians. This should include sophisticated in-depth research such as the euglycemic clamp studies. More mechanistic studies should be undertaken to better characterize the 'Asian Indian phenotype' with particular reference to studies on visceral fat and muscle. Finally, it would be worthwhile examining whether lifestyle changes can override genetic factors, and thus alter the Asian Indian phenotype.

CONCLUSION

The prevalence of type 2 diabetes is rising at an alarming rate in India and now exceeds the rates seen in migrant Indians in the USA, indicating a complete reversal of the scenario seen two or three decades ago. The phenotype of an Asian Indian with type 2 diabetes is different than Caucasians and characterized by higher body fat percentage, higher waist circumference or waist-to-hip ratio representing central obesity, rapid decline in beta cell function, and a greater degree of insulin resistance with higher risk for cardiovascular disease. Clearly, more studies are needed to characterize this unique 'Asian Indian Phenotype'. Finally, prevention and control of diabetes should become a public health priority in India. The time for action is NOW!

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Conflicts of interest

There are no conflicts of interest.

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- ■■ of outstanding interest

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