Diabetes mellitus and its complications in India

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Abstract | India is one of the epicentres of the global diabetes mellitus pandemic. Rapid socioeconomic development and demographic changes, along with increased susceptibility for Indian individuals, have led to the explosive increase in the prevalence of diabetes mellitus in India over the past four decades. Type 2 diabetes mellitus in Asian Indian people is characterized by a young age of onset and occurrence at low levels of BMI. Available data also suggest that the susceptibility of Asian Indian people to the complications of diabetes mellitus differs from that of white populations. Management of this disease in India faces multiple challenges, such as low levels of awareness, paucity of trained medical and paramedical staff and unaffordability of medications and services. Novel interventions using readily available resources and technology promise to revolutionise the care of patients with diabetes mellitus in India. As many of these challenges are common to most developing countries of the world, the lessons learnt from India's experience with diabetes mellitus are likely to be of immense global relevance. In this Review, we discuss the epidemiology of diabetes mellitus and its complications in India and outline the advances made in the country to ensure adequate care. We make specific references to novel, cost-effective interventions, which might be of relevance to other low-income and middle-income countries of the world.

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Diabetes mellitus, a chronic metabolic noncommunicable disease (NCD), has attained epidemic proportions worldwide. As of 2015, >415 million adults have diabetes mellitus, and this number is estimated to increase to 642 million by 2040 (REF. 1). More than 95% of all adults with diabetes mellitus have type 2 diabetes mellitus (T2DM). India is one of the epicentres of the global diabetes mellitus epidemic and has the second highest number of people with the disease in the world (~69 million individuals as of 2015)[1]. Other countries of the south Asian region, such as Bangladesh, Pakistan, Sri Lanka and Nepal, also have large numbers of individuals with diabetes mellitus[1]. In addition, countries such as the UK, the USA, Mauritius, Fiji, Malaysia, Singapore, South Africa and countries in the Gulf region of the Middle East are home to a large diaspora of Asian Indian individuals, who have been found to have a much higher prevalence of diabetes mellitus than the native populations of the respective countries[2–4].

Asian Indian people, which we broadly define as individuals originating from the Indian subcontinent (the countries of India, Pakistan, Bangladesh, Sri Lanka, Afghanistan, Nepal, Bhutan and the Maldives)[5] constitute >17% of the world's population and also have a specific phenotype, characterized by high levels of intra-abdominal fat and insulin resistance in spite of a low BMI, which predisposes them to T2DM and premature coronary heart disease[6]. Learning about the patterns and behaviour of diabetes mellitus in this ethnic group is of the utmost importance. Fortunately, in parallel with the increase in the prevalence of diabetes mellitus in India, research activities on this disease and its complications have increased. In this Review, we discuss the epidemiology and unique features of diabetes mellitus and its complications in India. We will also highlight the major challenges in the delivery of optimal care for patients with diabetes mellitus and suggest possible solutions.

Epidemiology

The first formal studies to evaluate the prevalence of diabetes mellitus in India did not occur until the middle of the twentieth century. By the end of the 1960s, seven studies had been published detailing the prevalence of the disease[7–12]. Subsequently, numerous single-centre and multicentre studies on the epidemiology of diabetes mellitus in various parts of the country have been published. Notwithstanding the caveat that these studies have used varying methodologies, sampling

Key points

- Asian Indian individuals have a high predisposition to type 2 diabetes mellitus (T2DM), which develops at a younger age and lower BMI than in western countries
- Asian Indian people with T2DM tend to have a higher risk of coronary artery disease and, possibly, a lower risk of microvascular complications compared with white individuals
- Since the 1960s, the prevalence of diabetes mellitus in India has increased in both the urban and rural areas of the country and has spread to involve individuals from all socioeconomic strata
- Management of diabetes mellitus in India faces many challenges but novel interventions using readily available resources and technology promise to revolutionise care
- Understanding how India deals with diabetes mellitus can help other low-income and middle-income countries in the treatment of this devastating disease

techniques and diagnostic criteria, their results suggest a clear increasing trend in the prevalence of diabetes mellitus. For example, this trend has been most markedly visible in the southern Indian city of Chennai, where the results of a series of studies conducted from 1989 to 2004 showed a 72% increase in the prevalence of the disease[13] (FIG. 1; Supplementary information 1 (Figure)).

The first multicentre study on diabetes mellitus in India was initiated by the Indian Council of Medical Research (ICMR) in 1971. This study estimated the prevalence of diabetes mellitus in six cities and surrounding villages in India (Ahmedabad, Kolkata, Cuttack, Delhi, Pune and Trivandrum). The prevalence of the disease were found to be 2.1% in the urban areas and 1.5% in the rural areas[14]. More than two decades later, the National Urban Diabetes Study sampled individuals from six major metropolitan cities of India and reported prevalences ranging from 9.3% in Mumbai to 16.6% in Hyderabad[15] (FIG. 1). At around the same time, the Prevalence of Diabetes in India study evaluated the prevalence of diabetes mellitus in small towns and villages of India, which was found to be 5.9% and 2.7%, respectively[16].

Until 2011, prevalence estimates for diabetes mellitus in India from the International Diabetes Federation (IDF) were based on the results of these, and other smaller, studies[17]. However, none of these studies could be considered fully representative of India as a whole. For instance, the National Urban Diabetes Study omitted the rural areas completely and the Prevalence of Diabetes in India Study did not study the large metropolitan cities.

The ongoing ICMR–India Diabetes (ICMR–INDIAB) study aims to address this knowledge gap by estimating the prevalence of diabetes mellitus in India, using uniform sampling techniques and diagnostic criteria in a representative sample of individuals from rural and urban areas of all 29 states of India[18]. From the results of phase I of the study (covering four regions of the country: Tamil Nadu, Maharashtra, Jharkhand and Chandigarh), it was estimated that 62 million individuals had diabetes mellitus and 77 million had prediabetes (that is, impaired glucose tolerance and impaired fasting glucose according to the WHO criteria) in India in 2011 (REF. 19). These results led the IDF to revise their estimates of the number of people with the disease in India from 50 million (in the 2009 edition of the IDF Atlas) to 61.9 million (in the 2011 edition)[20]. These numbers are, of course, not static; and the 2015 update of the Atlas estimates that 69.2 million people in India will have diabetes mellitus[1]. TABLE 1 outlines some of the single-centre studies on the prevalence of diabetes mellitus in India, and TABLE 2 (REFS 14–16,19) shows the multicentre studies in which a definite increase in prevalence of diabetes mellitus was observed over time.

What are the most likely reasons for such a huge increase in the prevalence of diabetes mellitus in India? Have diagnostic criteria changed; is sampling and detection better; is the increase in population with improved longevity and demographic changes a factor; have risk factors for the disease increased; or are lifestyle changes leading to obesity, unhealthy diet and physical inactivity? In all likelihood, all of these factors probably contribute to the prevalence of the disease, and identifying the individual causes is difficult. More detailed studies need to be done to understand the impact of each of these factors on the rising diabetes mellitus epidemic in India.

Are Asian Indian people more prone to T2DM?

Migrant Asian Indian individuals in various parts of the world such as Mauritius, Fiji and the UK[2–4], have a higher prevalence of T2DM than the native populations of those countries[3,4,21–28] (TABLE 3). In addition, studies conducted in the past few years have reported that the incidence of T2DM in Asian Indian people is among the highest in the world, exceeded only by some isolated and homogenous populations such as the Pima Indian people and the Pacific Islanders of Nauru[29].

This increased propensity to develop T2DM occurs despite Asian Indian individuals being younger, and in many cases leaner, than non-Indian counterparts when diagnosed with the disease in these studies[30]. In a study of 24,335 individuals from 11 countries, Asian Indian people were found to have the highest prevalence of diabetes mellitus, and the peak prevalence of the disease was reached ~10 years earlier in Asian Indian individuals compared with Chinese people and Japanese people[31]. According to the ICMR–INDIAB study, the 'take-off point' for increased prevalence of T2DM among Asian Indian individuals is 25–34 years, clearly a decade or two earlier than in western populations[19]. These findings have led to the concept of a specific 'Asian Indian phenotype', a collection of clinical and biochemical features that dispose Asian Indian people to a higher risk of T2DM than individuals from other major ethnic groups (FIG. 2)[6]. For example, for a given BMI, Asian Indian individuals have higher waist circumference, higher waist-hip ratios, more subcutaneous and visceral fat and more insulin resistance than individuals of European origin[32]. Asian Indian people also have a high prevalence of the metabolic syndrome (20–32%)[33] with some specific findings as outlined here[34]. Asian Indian people have been consistently

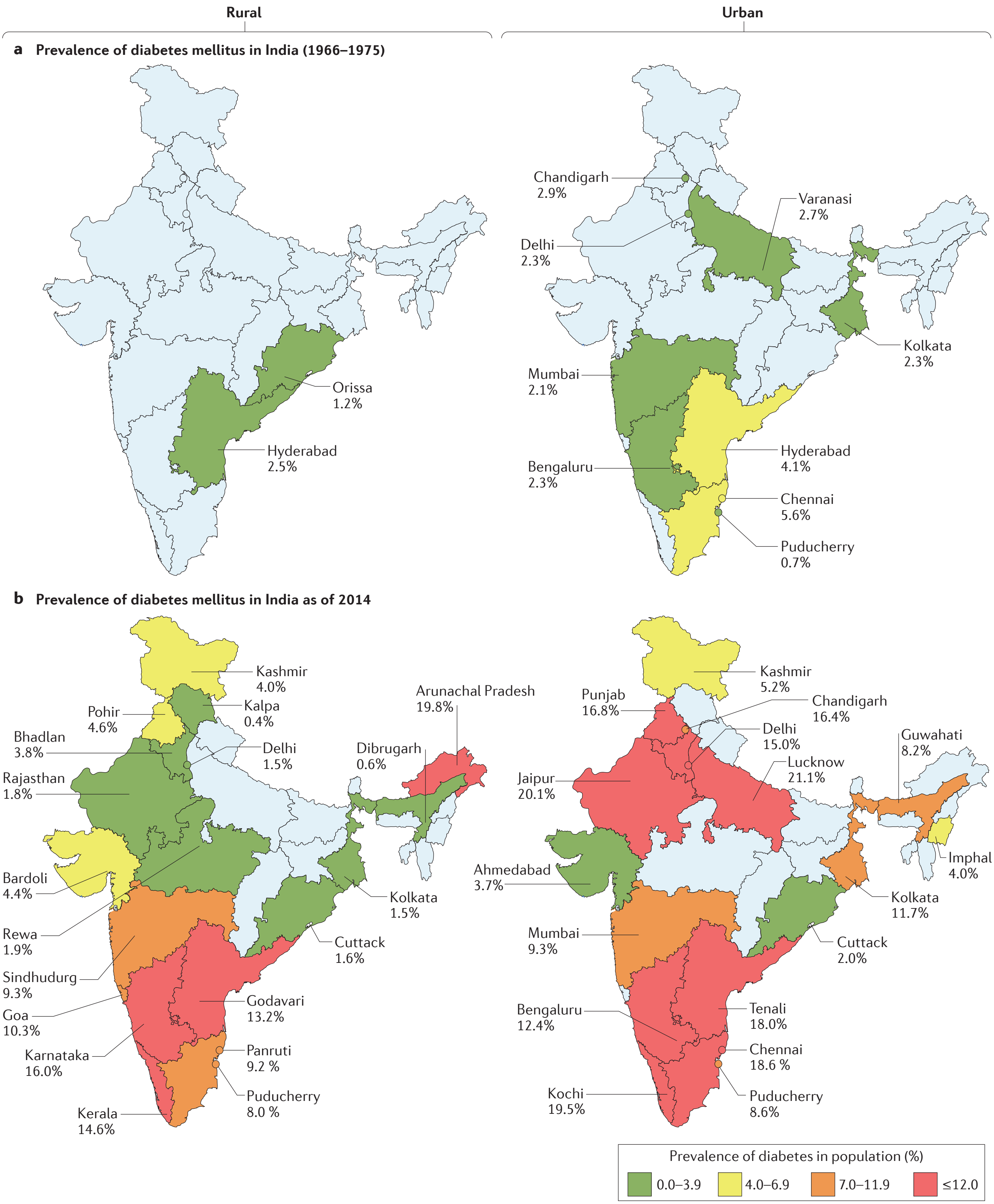

Figure 1 | **The changing prevalence of diabetes mellitus in India. a** | The prevalence of diabetes mellitus in rural and urban populations in India between 1966 and 1975. **b** | The prevalence of diabetes mellitus in rural and urban populations in India in 2014. These figures do not differentiate between different types of diabetes mellitus; however, according to the International Diabetes Foundation Atlas ~95% of adult individuals with the disease have type 2 diabetes mellitus. An expanded version of this figure is included in Supplementary information S1 (figure).

Table 1 | **Single-centre studies showing prevalence of diabetes mellitus in India**

Location	Year	Urban				Rural			
		n	Age (years)	Method of diagnosis	Prevalence (%)	*n*	Age (years)	Method of diagnosis	Prevalence (%)
Northern region									
Chandigarh[17]	1966	3,846	≥30	US	2.9	–	–	–	–
Varanasi[17]	1966	2,572	≥10	US	2.7	–	–	–	–
Lucknow[17]	1973	2,190	≥20	RBG	1.1	–	–	–	–
Delhi[17]	1974	2,783	≥15	RBG	2.3	–	–	–	–
Delhi[17]	1974	2,291	≥20	RBG	2.7	–	–	–	–
Delhi[17]	1986	6,878	≥20	K	3.1	–	–	–	–
Haryana[17]	1986	–	–	–	–	3,374	≥10	RBG	3.8
Rewa[17]	1988	–	–	–	–	15,000	-	RBG	1.9
Punjab[17]	1994	–	–	–	–	1,100	≥30	K, PG	4.6
Srinagar[17]	2000	1,538	≥40	K, F, PG*	5.2	4,045	≥40	-	4.0
Delhi[17]	2001	532	≥18	K, F	10.3	–	–	–	–
Jaipur[17]	2003	1,091	≥20	K, F	12.3	–	–	–	–
Punjab[17]	2004	458	≥20	K, F	16.8	–	–	–	–
Rajasthan[17]	2004	–	–	–	–	782	≥20	–	–
Delhi[17]	2005	2,122	20-59	K, F, PG	15.0	–	–	–	–
Jaipur[17]	2007	1,127	≥20	K, F	20.1	–	–	–	–
Nagpur[17]	2007	–	–	–	–	924	≥30	K, F, PG	3.7
Rajasthan[17]	2007	–	–	–	–	2,099	≥20	-	1.7
Lucknow[17]	2008	1,112	≥30	K, F, PG	21.1	–	–	–	–
Chandigarh[149]	2011	2,227	≥20	K, F, PG*	11.1	–	–	–	–
Jaipur[150]	2012	739	30–59	K, F	13.4	–	–	–	–
Southern region									
Hyderabad[17]	1966	21,396	≥20	US	4.1	–	–	–	–
Chennai[17]	1966	5,030	≥20	US	5.6	–	–	–	–
Pondicherry[17]	1968	2,694	≥20	US	0.7	–	–	–	–
Hyderabad[17]	1972	–	–	–	–	2,006	≥20	US	2.4
Hyderabad[17]	1972	–	–	–	–	847	≥10	RBG	2.5
Bangalore[17]	1973	25,273	≥5	RBG	2.3	–	–	–	–
Tenali[17]	1984	848	≥15	RBG	4.7	–	–	–	–
Kudremukh[17]	1988	678	≥20	K, F, PG	5.0	–	–	–	–
Eluru[17]	1989	5,699	≥0	K	1.5	3,864	≥0	K	1.9
Gangavati[17]	1990	-	-	-	-	765	≥30	K, F, PG	2.2
Chennai[17]	1992	900	≥20	K, F, PG*	8.2	1,038	≥20	K, F, PG*	2.4
North Arcot[17]	1994	–	–	–	–	467	≥40	K, PG*	4.9
Chennai[17]	1997	2,183	≥20	K, F, PG	11.6	–	–	–	–
Chennai[17]	1999	1,198	NA	K, F, PG	7.6	–	–	–	–
Trivandrum[17]	2000	619	≥20	RBG*, F, PG	16.9	–	–	–	–
Trivandrum[17]	2000	206	≥19	K, PG	16.3	–	–	–	–
Chennai[17]	2000	26,066	≥20	K	2.9	–	–	–	–
Chennai[17]	2001	1,262	≥20	K, F, PG	9.3	–	–	–	–
Chennai[17]	2006	2,350	≥20	K, F, PG	14.3	–	–	–	–
Godavari[17]	2006	–	–	–	–	4,535	≥30	F*	13.2
Kochi[17]	2006	3,069	18-80	K, PG*	19.5	–	–	–	–

Table 1 (cont.) | **Single-centre studies showing prevalence of diabetes mellitus in India**

Location	Year	Urban				Rural			
		n	Age (years)	Method of diagnosis	Prevalence (%)	*n*	Age (years)	Method of diagnosis	Prevalence (%)
Southern region (cont.)									
Tamil Nadu[17]	2008	• 2,192 (metro)[#] • 2,290 (town)	≥20	K, F, PG	• 18.6 • 16.4	2,584	≥20	K, F, PG	9.2
Kerala[151]	2009	–	–	–	–	1,990	≥18	K, F	14.6
Coastal Karnataka[152]	2010	–	–	–	–	1,239	≥30	K, RBG, F*	16
Kolar[153]	2010	–	–	–	–	311		K, F*	10
Puducherry[154]	2011	686	≥20	K, F	8.6	684	≥20	K, F	8.04
Tenali[155]	2012	534	≥20	K, F, PG	18	–	–	–	–
Chennai[156]	2015	2,305	40–84	K, F, PG	38.0	–	–	–	–
Eastern region									
Orissa[17]	1971	–	–	–	–	2,447	≥10	RBG	1.2
Kolkata[17]	1975	4,000	≥20	RBG	2.3	–	–	–	–
Guwahati[17]	1998	1,016	≥20	K, PG	8.2	–	–	–	–
Manipur[17]	2001	1,664	≥15	K, PG	4.0	–	–	–	–
Kolkata[157]	2008	2,160	≥20	K, F*	11.5	–	–	–	–
Manipur[158]	2013	1,768	≥20	F or PG	16.6	–	–	–	–
West Bengal[159]	2013	1,817	20–59	K, F, PG	15.0	–	–	–	–
Arunachal Pradesh[160]	2014	–	–	–	–	1,370	≥20	K, F, PG	19.8
Western region									
Mumbai[17]	1963	18,243	≥20	US	1.5	–	–	–	–
Mumbai[17]	1966	3,200	≥20	RBG	2.1	–	–	–	–
Ahmedabad[17]	1978	3,516	≥15	RBG	3.0	–	–	–	–
Bhadlan[17]	1986	–	–	–	–	3,374	≥10	RBG	3.8
Bardoli[17]	1987	–	–	–	–	1,348	All	RBG	4.4
Mumbai[17]	2001	520	≥20	K, F, PG	7.5	–	–	–	–
Sindhudurg[17]	2006	–	–	–	–	1,022	≥20	K, F, PG	9.3
Goa[161]	2011	–	–	–	–	1,266	≥30	K, F	10.3

*Capillary blood glucose method. [#]Metro refers to the city of Chennai; town refers to the smaller urban areas of the state. F, fasting blood glucose; K, known diabetes mellitus; PG, post-glucose load; RBG, random blood glucose; US, urine sugar.

shown to have higher fasting insulin levels than white individuals[35,36]. Indeed, hyperinsulinaemia has even been detected in the cord blood of otherwise healthy Asian Indian infants, even though they were on average lighter than their white counterparts[37]. Exposure to high levels of insulin resistance from early in life is thought to render the pancreatic β cell less capable of compensating for the decline in insulin sensitivity that normally occurs with age, which might contribute to the early development of hyperglycaemia and T2DM[38]. In a 2013 study from southern India, β-cell dysfunction (as measured by the insulin disposition index) was found to be prominent in Asian Indian patients with even mild dysglycaemia (that is, impaired fasting glucose, impaired glucose tolerance or both)[39].

What could be the reason for the development of this unhealthy phenotype in a substantial proportion of one of the world's largest ethnic groups? Investigators in several studies have tried to assess the role of population-specific genetic and epigenetic factors in the predisposition of Asian Indian people to T2DM. However, the paucity of large-scale genome-wide association studies (GWAS) in the Asian Indian population prevents any firm conclusions. Of the GWAS that have been conducted in Asian Indian populations many, but not all, of the susceptibility loci for T2DM identified in European populations have been found. For example, a GWAS in an Asian Indian population (the results of which were published in 2011) identified six novel T2DM susceptibility loci (in *GRB14*, *ST6GAL1*, *VPS26A*, *HMG20A*, *AP3S2* and *HNF4A*)[40]. In a population of 2,465 individuals belonging to two ethnic groups in India comprising 7,221 Indo-Europeans and 2,849 Dravidians from New Delhi, Jaipur and Chennai, the *TMEM163* gene was shown to have a genome-wide significant association with T2DM[41]. In a GWAS of

Table 2 | **Multicentre studies showing the prevalence of diabetes mellitus in India**

Location	Year	Urban			Rural		
		n	Method of diagnosis	Prevalence (%)	*n*	Method of diagnosis	Prevalence (%)
Ahmedabad[14]	1979	3,496	K, PG*	3.7	3,496	K, PG*	3.74
Kolkata[14]	1979	3,488	K, PG*	1.8	3,488	K, PG*	1.8
Cuttack[14]	1979	3,849	K, PG*	2.0	3,849	K, PG*	2.0
Delhi[14]	1979	2,358	K, PG*	0.9	2,358	K, PG*	0.9
Pune[14]	1979	2,796	K, PG*	1.9	2,796	K, PG*	1.9
Trivandrum[14]	1979	3,090	K, PG*	1.8	3,090	K, PG*	1.8
Delhi[15]	2001	2,300	K, F, PG*	11.6	–	–	–
Bangalore[15]	2001	13,559	K, PG*	12.4	–	–	–
Chennai[15]	2001	1,668	K, PG*	13.5	–	–	–
Hyderabad[15]	2001	1,427	K, PG*	16.6	–	–	–
Kolkata[15]	2001	2,378	K, PG*	11.7	–	–	–
Mumbai[15]	2001	2,084	K, F, PG*	9.3	–	–	–
National[#] (REF. 16)	2004	21,516	F*	4.6	19,754	F*	1.9
Tamil Nadu[19]	2011	1,029	K, PG*	13.7	2,480	K, PG*	7.8
Maharashtra[19]	2011	1,093	–	10.9	2,476	–	6.5
Jharkand[19]	2011	840	–	13.5	2,051	–	3.0
Chandigarh[19]	2011	839	–	14.2	2,247	–	8.3

*Capillary blood glucose method. #Delhi, Bangalore, Chennai, Hyderabad, Kolkata and Mumbai excluded, only smaller towns and villages sampled. F, fasting blood glucose; K, known diabetes mellitus; PG, post-glucose load; RBG, random blood glucose.

Punjabi Sikh individuals from India, a single nucleotide polymorphism within the *SGCG* gene had significant genome-wide association with T2DM[42]. Notably, certain genotypes (such as the Pro12Ala polymorphism of the *PPARγ* gene) that protect against development of T2DM in white individuals, do not seem to do so among Asian Indian patients[43]. Considering the vast ethnic diversity of India, more GWAS need to be performed from other parts of the country to elucidate the genetic basis of T2DM in this population.

Although genetic factors undoubtedly predispose Asian Indian people to the development of T2DM, the explosion in the prevalence of this disease in India over the past four decades cannot be fully explained by these factors alone — major changes in the genetic makeup of a population cannot occur within such a short time span. Environmental factors seem to have a far more important role in the development and propagation of the T2DM epidemic in India. In this context, the role of early life (or antenatal) factors is important. Maternal malnutrition (and its attendant consequence of small-for-gestational age babies) has been suggested as a major driver of the diabetes mellitus epidemic in India. Infants born to undernourished women have higher levels of adiposity in spite of their small size than infants born to adequately nourished mothers[44]. Low maternal levels of vitamin B_{12}, particularly when coupled with normal to high folate levels, are associated with adiposity and insulin resistance in the offspring[45]. Maternal undernutrition has also been associated with diminished β-cell mass in experimental animals, but to what extent this finding applies to humans is unclear[46]. Small-for-gestational age babies who experience rapid weight gain (known as adiposity rebound) after the age of 2 years have a particularly high risk of developing impaired glucose tolerance during adolescence[47]. The accelerated increase in BMI in children in India has been suggested to be a fairly new phenomenon, driven by the process of nutrition transition, and this upward trajectory of BMI starting in early childhood might explain, at least in part, the current epidemic of T2DM in India.

In the past 40 years, and particularly since economic liberalization in 1991, the lifestyle of the average Asian Indian person has undergone far-reaching changes. Vehicle ownership has more than quadrupled, mobile telephones and computers have become widespread and occupations have become more sedentary and less labour-intensive than in previous years[48]. These developments have led to a drastic decline in occupational physical activity levels of people in India, which has not been compensated for by an increase in the levels of recreational physical activity. In fact, data show that <10% of the Indian population performs any recreational physical activity at all[49]. Improvement in food security and increased disposable income have shifted the consumption patterns of Indian individuals away from coarse grains and millets to highly refined white rice and wheat flour as a staple[50]. In a study in the urban population of Chennai, India, individuals in the highest quartile of refined cereal intake were found to have 7.83-fold higher odds of developing the metabolic

Table 3 | **Prevalence of diabetes mellitus in Asian Indian diaspora**

Location	Prevalence in Asian Indian population	Prevalence in reference population	Study
Fiji	• 10.2% (rural men) • 8.3% (urban men) • 9.6% (rural women) • 11.8% (urban women)	• 5.7% (rural men) • 7.3% (urban men) • 8.5% (rural women) • 13.2% (urban women)	Zimmet *et al.* (1983)[4]
Fiji	• 17.9% (men) • 19.9% (women)	• 11.1% (men) • 13.6% (women	Lin *et al.* (2015)[28]
Trinidad	• 10.0% (men) • 11.6% (women)	• 5.8% (African) • 4.3% (European) • 7.4% (Individuals of mixed race) • 15.8% (African) • 10.9% (European) • 14.3% (Individuals of mixed race)	Beckles *et al.* (1986)[21]
UK	• 11.2% (men) • 8.9% (women)	• 2.8% (white men) • 4.2% (white women)	Simmons *et al.* (1989)[22]
Mauritius	• 12.4% (Hindu Indians) • 13.3% (Muslim Indians)	• 11.9% (Chinese) • 10.4% (Creole)	Dowse *et al.* (1990)[3]
South Africa	• 13%	• 5.2–6.0% (black individuals) • 3% (white individuals)	Omar and Motala (1996)[23]
USA	• 6.8% (normal weight) • 8.8% (overweight) • 32.9% (obese)	• 2.4% (normal weight)* • 4.4% (overweight)* • 10.8% (obese)*	Oza-Frank *et al.* (2009)[24]
USA	• 10.0% (migrants from south Asia)	• 3.1% (migrants from Europe)	Oza-Frank and Narayan (2010)[25]
Singapore	• 17.2%	• 16.9% (Malaysian) • 9.7% (Chinese)	National Registry of Diseases Office (2011)[26]
Malaysia	• 37.9%	• 23.8% (Malaysian) • 18.4% (Chinese)	Wan Nazaimoon *et al.* (2013)[27]

*Specifically non-Latin American, white individuals.

syndrome and a 7.9% increased prevalence of elevated fasting levels of glucose compared with individuals in the lowest quartile[51]. In addition, increased consumption of junk food and beverages sweetened with sugar has the potential to further accelerate the development of diabetes mellitus.

Although these changes are still not as profound in the rural areas of India as in the cities, individuals living in rural communities are fast catching up with those in urban areas. Another important factor is large-scale migration of rural dwellers into cities in search of better opportunities. For example, in some studies, these rural-to-urban migrants have been shown to have a much higher prevalence of diabetes mellitus than their kin who stayed behind in the villages (14.3 versus 6.2%, respectively)[52].

Considering these developments, the finding that the prevalence of obesity and overweight are disturbingly high in many parts of India is unsurprising[53,54], even among schoolchildren[55]. As noted earlier in the text, being overweight in childhood and adolescence probably adds to the risk of insulin resistance conferred by low birth weight and sets the stage for development of T2DM by early adulthood.

In fact, Asian Indian people living in their native country now, for the first time, have a higher prevalence of T2DM than their counterparts who have moved abroad (for example, to the USA), with an age-adjusted prevalence among adults aged 40–84 years of 38% compared with 24% in those who have emigrated[56]. This finding indicates that the epidemic of T2DM is now firmly established in India and that the numbers can be expected to further increase in the near future. Even more worryingly, within India, T2DM seems to be moving into the lower income groups, who cannot afford to pay for monitoring and treatment[57,58].

Other forms of diabetes mellitus

Type 1 diabetes mellitus

Type 1 diabetes mellitus (T1DM) is uncommon in India compared with western nations. Nevertheless, the incidence is higher than in many other Asian countries, including China; estimates indicate that every fifth child in the world with T1DM is Indian, compared with every seventh adult with T2DM[1,59].

The IDF estimates that three new cases of T1DM per 100,000 children aged 0–14 years occur in India every year[1]. Wide regional variation seems to exist, with studies from Karnataka, Chennai and Karnal (a district in the state of Haryana) reporting incidence rates of 17.93, 3.2 and 10.2 cases per 100,000 children, respectively[60–62]. However, these numbers are higher than the estimated incidence in China (0.1 per 100,000), but still low compared with European regions such as Sardinia and Finland (36.8 and 36.5 per 100,000, respectively)[63].

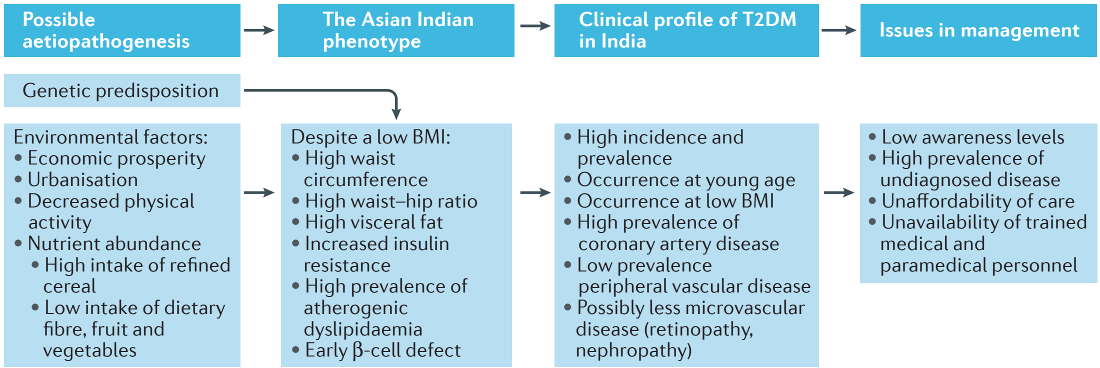

Figure 2 | **Distinctive features of T2DM in India.** The Asian Indian phenotype can lead to increased prevalence of T2DM, which has a unique clinical profile. Patients with T2DM in India also have unique management challenges.

T1DM in India tends to be infrequently associated with positive titres of pancreatic autoantibodies and is therefore classified as idiopathic (T1b) diabetes mellitus[64]. The human leukocyte antigen (HLA) associations with T1DM are also different in Asian Indian individuals compared with those described for white populations. For example, in a study of North Indian children with T1DM, the haplotypes A26-B8-DRB1*03 and Ax-B50-DRB1*03 were encountered most frequently (found in 25% each of patients). The classic haplotype A1-B8-DRB1*03 that favours autoimmunity in white individuals was found only in a minority (7.2%) of this Asian Indian population[65].

Monogenic diabetes mellitus

Few data exist on the prevalence of monogenic forms of diabetes mellitus in India. In a series of 96 unrelated patients diagnosed with monogenic diabetes of the young (MODY) according to the clinical criteria of Tattersall and Fajans[66], 9% were found to have mutations in *HNF1A* (previously known as *MODY3*) and 3.4% in *HNF4A* (previously known as *MODY1*)[67,68]. In another study from southern India, 11 mutations were found in 56 patients with clinically diagnosed MODY, of which seven were novel mutations[69]. Efforts to elucidate the clinical picture of monogenic diabetes mellitus in India are limited by the paucity of specialized genetic testing facilities and the considerable expenses involved.

Fibrocalculous pancreatic diabetes mellitus

Fibrocalculous pancreatic diabetes mellitus (FCPD) is an uncommon form of diabetes mellitus secondary to chronic calcific nonalcoholic pancreatitis[70]. FCPD used to be encountered in the southern parts of India (particularly in the states of Kerala and Tamil Nadu). However, the prevalence seems to be declining even in these states; in a series from Chennai, patients with FCPD constituted 1.6% of all patients with diabetes mellitus between 1991 and 1995, but only 0.2% between 2006 and 2010 (REFS 71,72). Patients with FCPD have recurrent episodes of abdominal pain and oily stools and an abdominal radiograph reveals pancreatic calculi[70]. These patients are as prone to developing microvascular complications as individuals with T2DM; however, macrovascular disease seems to be uncommon. In a study from southern India that compared the prevalences of diabetes mellitus complications in individuals with FCPD and those with T2DM, prevalences were similar for nephropathy (10.1% versus 15.0%), retinopathy (30.1% versus 37.2%) and neuropathy (20.9% versus 25.3%), but the prevalence of coronary artery disease was substantially lower (5.1% versus 11.9%)[73].

Malnutrition-modulated diabetes mellitus is similar to FCPD, but without the pancreatic calculi[74]. Its existence was first reported from the eastern parts of India (the states of Orissa and Bihar) but the lack of definitive criteria for its diagnosis makes this a dubious entity. The exact aetiology of this condition remains obscure, although an autoimmune mechanism has been postulated[74]. The currently accepted classification of diabetes mellitus does not include malnutrition-modulated diabetes mellitus[75].

Gestational diabetes mellitus

The prevalence of gestational diabetes mellitus (GDM) in a population is proportional to that of T2DM and impaired glucose tolerance[76]. Unsurprisingly, therefore, the prevalence of GDM is rapidly increasing in India. Studies in the early 1980s on this condition reported a prevalence of 2% in India[77]. By 2008, investigators were reporting a prevalence of 17.8% in urban areas, 13.8% in semi-urban areas and 9.9% in rural areas[78]. Moreover, wide regional variation exists in the prevalence of GDM in India, with the lowest rates (3.8%) being noted in Kashmir[79], and the highest (16.2%) in Tamil Nadu[78].

Women who have had GDM are at sevenfold higher risk of developing T2DM in the future than those with normal glucose tolerance during pregnancy[80]. Moreover, T2DM has been suggested to occur more frequently and at a faster rate among Asian Indian people than in other ethnic groups (for example, a 50% conversion rate within 5 years is seen in Asian Indian people, compared with <20% for non-Latin American white individuals)[81–83]. Education regarding diet, physical activity and regular screening can delay or prevent the development of T2DM in these women. Similarly, children born to mothers with GDM are prone to develop obesity and T2DM later in life[84]. Encouraging the adoption of healthy lifestyle practices in these children can prevent them from developing diabetes mellitus[85]. Such healthy lifestyle practices are of particular importance in the Asian Indian population, in whom the background risk of T2DM is already high. Prompt diagnosis, appropriate management and close follow-up of women with GDM and their offspring has the potential to prevent diabetes mellitus in two generations and to disrupt the vicious intergenerational cycle of the disease.

Complications in India

The microvascular and macrovascular complications of diabetes mellitus account for most of the morbidity and mortality associated with the disease. While poor glycaemic control and long duration of illness seem to be the most important risk factors for these complications, evidence suggests that ethnic variability in the susceptibility to the complications might also exist.

Microvascular complications

In studies on the prevalence of diabetic retinopathy in India, a lower prevalence compared with western populations has consistently been seen[86,87]. In the population-based Chennai Urban Rural Epidemiology (CURES) cohort, the prevalence of retinopathy in patients with self-reported diabetes mellitus was 17.6%[88], and very similar figures were reported by two other studies from other regions in India[87,89]. Most studies conducted in western populations have found a retinopathy prevalence of more than 30% in individuals of similar age and duration of disease[90]. In these three studies the risk factors for developing diabetic retinopathy were duration of diabetes mellitus and poor glycaemic control.

Migrant Asian Indian populations have a higher prevalence of diabetic nephropathy than native populations of the concerned countries[91–93]. For instance, in a multiethnic population in the UK, proteinuria was found in 32% of Asian Indian men and 21% of women with diabetes mellitus compared to 14% and 9% of white men and women respectively[94]. Similarly, in a cohort study conducted among patients with diabetes mellitus in the Netherlands, individuals of Asian Indian ancestry had 3.9 higher odds of developing albuminuria, and a 1.45 times higher rate of reduction in glomerular filtration rate than individuals of European ancestry[93]. However, data from India present a mixed picture. The clinic prevalences of microalbuminuria and frank nephropathy (36.3% and 6.9% respectively) are similar to those reported in the migrant studies noted above[94–96]. However, in the population-based CURES cohort a much lower prevalence of frank nephropathy (2.2%) was reported, although the prevalence of microalbuminuria was similar to that found in the other studies[97]. Notwithstanding these lower prevalence rates, the numbers of individuals reaching end-stage renal disease as a result of diabetic nephropathy is likely to substantially increase in the near future, on account of the sheer number of people with diabetes mellitus in India. That few of these individuals will be able to afford chronic dialysis or kidney replacement, the only two effective modalities of treatment for end-stage renal disease, is of great concern[98].

From the available literature, the prevalence of neuropathy varies greatly depending on the definition of neuropathy applied and the diagnostic tests used. For example, in a study from south India, 19.5% of individuals with newly diagnosed T2DM had neuropathy compared with 27.8% of those with known disease[99]. In another study from northeastern India, the reported prevalence of neuropathy was 29.5% in newly diagnosed patients with T2DM[100], while other investigators have reported a prevalence of 29.2% among recently diagnosed patients in Lucknow[101]. In studies conducted in multiethnic populations in the UK, Asian Indian individuals were found to have significantly lower rates of large-fibre and small-fibre neuropathy compared with individuals of European ethnicity (OR 0.58; 95% CI 0.37–0.92; $P<0.02$)[102]. Improved skin microvascularisation has been postulated as the reason for the reduced prevalence of neuropathy[102]. However, in other studies from the same investigators, these findings have been challenged. Although Asian Indian people tend to have lower rates of peripheral neuropathy than white individuals and individuals of Afro-Caribbean descent, they had 50% higher risk of painful neuropathy symptoms[103].

Macrovascular complications

More than 65% of patients with T2DM die of cardiovascular disease; of these, nearly 80% are attributable to coronary artery disease (CAD)[104]. The susceptibility of Asian Indian individuals to CAD is well known[105]. Compared with white individuals, CAD tends to develop a decade or two earlier and triple vessel disease is more common; mortality after an acute coronary event is also 40% higher in Asian Indian patients[106]. The presence of T2DM seems to confer a 3–4 times higher risk of cardiovascular disease to Asian Indian individuals than to their white counterparts, even after adjusting for sex, age, smoking status, hypertension and obesity[107]. Possible explanations include the atherogenic milieu promoted by high levels of insulin resistance and the high prevalence of 'atherogenic dyslipidaemia' characterized by high levels of triglycerides and small dense LDL cholesterol, and low levels of HDL cholesterol[108].

However, few population-based data exist on the prevalence of CAD in India, particularly comparing people with and without T2DM. In the Chennai Urban Population Study, a population-based study conducted in two residential colonies in Chennai, in South India, CAD had a prevalence of 21.4% among individuals with T2DM, compared with 9.1% among those with normal glucose tolerance and 14.9% among those with impaired glucose tolerance[109].

Peripheral vascular disease (PVD) is fortunately rare among patients with diabetes mellitus in India. Younger age of onset and relatively low prevalence of smoking are perhaps responsible for the low prevalence of PVD. In the CURES cohort[110], the prevalence of PVD was 8.6%, compared with 23.5% among patients with T2DM in the UK[111] and 20–30% in the USA[112]. Increased age, female sex and duration of disease were all related to increased incidence of PVD[110].

Diabetic foot ulcers

Diabetic foot ulcers and infections are responsible for >30% of the hospitalisations related to diabetes mellitus[113]. 25% of people with diabetes mellitus are estimated to develop a foot ulcer during their lifetime[114]. Diabetic foot ulceration is also an expensive complication of diabetes mellitus, owing to both medical care and on account of time lost from work and loss of income and financial independence[115,116]. The majority (>80%) of foot ulcers in India arise in neuropathic feet, with only a third having vascular insufficiency[117], which, importantly, implies that most of these ulcers can be prevented with proper patient education on appropriate foot care.

Infections

India is facing a double disease burden, with both the persistence of communicable diseases and the emergence of NCDs. Communicable diseases such as typhoid, cholera, malaria and dengue continue to be rampant in many parts of India[118], but tuberculosis deserves special mention. Diabetes mellitus and tuberculosis have a bidirectional relationship. Approximately 25% of patients with tuberculosis are estimated to have diabetes mellitus[119], and tuberculosis occurs in up to 8% of patients with diabetes mellitus[120]. Tuberculosis in patients with diabetes mellitus might present with atypical features, such as predominant lower lobe involvement, and thereby delay the diagnosis. Also, cure rates of tuberculosis are lower in patients with diabetes mellitus than those with tuberculosis alone (treatment failure rates 4.2% versus 0.7%)[121]. Prompt diagnosis and initiation of antituberculous chemotherapy, along with achievement of tight glycaemic control, are essential to ensure cure and prevention of reactivation of tuberculosis.

Diabetes mellitus care in India

The epidemic of diabetes mellitus and associated NCDs threatens to derail much of the progress India has made in health care over the past four decades. In 2013, an average Indian patient with diabetes mellitus was estimated to have spent Indian Rs4,493 (US$95) a year on treatment expenses. The figure increased to Rs12,690 ($270) if renal disease was present and to Rs19,020 ($404) if diabetic foot disease was present[122]. The magnitude of this expense can be understood if one considers that the per capita income in India during 2013–2014 was only Rs74,920 ($1,570). Owing to low penetrance of health insurance, much of this expenditure is, therefore, borne by the patient.

Diabetes mellitus care in India has a long history. The first diabetes mellitus clinics began in the government sector in the late 1940s in Chennai and Kolkata[123]; the former continues to function uninterrupted to this day. In the early 1970s, the first private hospital solely devoted to patients with diabetes mellitus was founded. Today, most of the larger cities of the country are served by well-equipped clinics devoted to caring for patients with diabetes mellitus, which are staffed by experienced physicians and paramedical staff[124].

Unfortunately, the situation is different in rural areas. Although 75% of India's population lives in rural areas, only 25% of medical practitioners work there[124]. Specialists in diabetes mellitus (and many other fields) are almost exclusively found in urban areas. Even in urban areas, a shortage exists of trained specialists in diabetes mellitus care, endocrinologists and specialized paramedical staff such as educators, nurses and podiatrists[124]. The ICMR–INDIAB study assessed knowledge and awareness, using a questionnaire, of diabetes mellitus in four regions of India in individuals with and without the disease. In this study, awareness regarding diabetes mellitus and its complications is low even among individuals who have the disease[125]. In many parts of the country, particularly in rural areas, the prevalence of undiagnosed diabetes mellitus is high, with nearly three undiagnosed individuals for every known case[19]. Under these circumstances, that the quality of care for diabetes mellitus in India is patchy is unsurprising. In the population-based ICMR–INDIAB study only approximately a third of individuals with self-reported diabetes mellitus in India had good control of their disease as defined by levels of HbA_{1c} of <7%[126]. The situation is no better in the clinics; in the DiabCare India 2011 study conducted in 330 centres across, mean HbA_{1c} of the 6,168 patients studied was 8.9%[127], a figure unchanged from a decade ago[128].

The Government of India, taking cognizance of the growing burden of NCDs, launched the National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases & Stroke in 2010 (REF. 129). This programme aims to prevent and control NCDs through lifestyle changes, provide early diagnosis and treatment and to build capacity and train individuals within the public health setup to cope with the rising burden of NCDs.

However, diabetes mellitus in India is too large a problem for the government to tackle alone. In India, most medical care for this disease is provided by general practitioners in the private sector. Several initiatives have, therefore, been launched under the public–private partnership model to improve the knowledge base of these medical practitioners and thereby build capacity in care to improve the quality of diabetes treatment in India. For example, the Certificate Course in Evidence Based Diabetes Management (CCEBDM) and the Certificate Course in Gestational Diabetes Mellitus (CCGDM) and the newly launched Certified Course in Diabetic Retinopathy conducted in collaboration with the Public Health Foundation of India are three such schemes[130,131]. CCEBDM has trained >7,500 physicians in the management of diabetes mellitus, while CCGDM has trained >2,500 obstetricians and physicians in the management of GDM. The National Diabetes

Educators Program has also trained >2,500 educators to become links between doctors and patients and improve the quality of care[132].

The application of new technologies such as telemedicine has the potential to revolutionise care for patients with diabetes mellitus in hitherto underserved rural areas of India. For example, the Chunampet Rural Diabetes Prevention Project was undertaken in a cluster of 42 villages in and around the Chunampet village in the state of Tamil Nadu in southern India[133]. This population was screened for diabetes mellitus and its complications using a telemedicine approach equipped with retinal photography, Doppler imaging, biothesiometry and electrocardiography. A vehicle equipped with the necessary equipment toured villages in this area to screen and assess any complications at the patient's doorstep. Retinal photographs and other investigation reports were immediately transmitted to the main urban assessment centre via a satellite link. Consultants in the urban centre then assessed the reports and engaged with the patients on a real-time basis via the satellite link[134]. A rural centre was established to provide basic diabetes mellitus care for those individuals who required care beyond what could be provided by telemedicine alone. Following this intervention, mean HbA_{1c} decreased from $9.3 \pm 2.6\%$ to $8.5 \pm 2.4\%$ within 1 year and <5% of patients needed referral to tertiary care units[134]. The Chunampet Rural Diabetes Prevention Project is considered a successful model for screening and delivery of diabetes mellitus care and prevention to rural areas in India and other developing countries[135].

However, the high cost of conventional retinal fundus cameras is a major barrier to widespread screening for diabetic retinopathy in many parts of the world. The use of smartphones to diagnose diabetic retinopathy using low-cost technology developed in Bangalore, India, has the potential to make retinal screening accessible, affordable and easily available to people with diabetes mellitus not only in India, but also in other parts of the developing world[136]. Smartphone-based retinal screening using a fundus-on-phone camera is similar to conventional retinal photography in terms of sensitivity and specificity[136].

Prevention

In several randomized controlled trials, T2DM can be prevented in individuals at high risk of developing the disease using lifestyle modification, drugs or a combination of the two[137–139]. However, most of these studies have been performed in developed nations such as the USA and Finland where sufficient resources can translate these findings into a real-life setting[136,137]. Moreover, and as noted earlier in the text, the nature of T2DM seems to be different in Asian Indian individuals, suggesting that such treatments might not be strictly applicable to this population. The need for prevention of T2DM in India has also been elegantly summarized in another review[140].

The investigators of a population-based cohort study have attempted to assess the population attributable risk of diabetes mellitus contributed by common modifiable risk factors in a south Indian population[139]. In that study, 80% of incident T2DM could be prevented by favourably modifying five risk factors — unhealthy diet, physical inactivity, abdominal obesity, high levels of triglycerides and low levels of HDL cholesterol[141]. In the Indian Diabetes Prevention Programme, patients with prediabetes were randomly assigned to receive intensive lifestyle modification, metformin or routine care[142]. At the end of a median follow-up period of 30 months, lifestyle modification was found to reduce the risk of T2DM by 28.5% (compared with 58% in the Diabetes Prevention Program in the USA) and metformin by 26.4% (versus 31%)[142]. Cost-effectiveness to prevent one case of T2DM with lifestyle modification was Rs47,341 ($1,052), with metformin, Rs49,280 ($1,095), and with the combined intervention, Rs61,133 ($1,359)[143]. Investigators in the ongoing Diabetes–a Community Lifestyle Intervention Programme are assessing the feasibility and effectiveness of a culturally tailored and appropriate lifestyle intervention programme in preventing T2DM in individuals with prediabetes[144].

An interesting preventive approach is the use of mobile-phone based messaging to enable lifestyle changes that might help prevent the development of T2DM. This intervention makes use of the high penetrance of mobile phones (nearly 80% overall, and close to 50% in rural areas)[145] in India and seems to be a promising approach for the future[146]. In an urban population in south India, provision of lifestyle advice through frequent mobile phone messages was associated with a significant reduction in incident T2DM (HR 0.64, 95% CI 0.45–0.92; $P = 0.015$) over 3 years, compared with control individuals who received only standard lifestyle advice at the baseline visit[146].

Ultimately, prevention of T2DM needs to be multisectoral and depends on the involvement and collaboration of many stakeholders such as patients, family, health-care providers and government agencies. Governmental policy decisions that might have an effect on minimizing the risk of developing both T2DM and other metabolic NCDs include: provision of adequate facilities for recreational physical activity; encouraging use of walking or cycling rather than mechanized transport; as well as discouraging consumption of junk food through taxation. Moreover, governments can help ensure the availability of healthy foods such as fresh fruit and vegetables at affordable prices and encourage healthy eating practices in schools. In combination with efforts at awareness creation, these steps will ensure adoption of healthier lifestyles by a wider section of the population and significantly reduce the risk of development of T2DM.

Relevance of the Indian experience

India is the prototypical underdeveloped nation that has undergone a dramatic socioeconomic and demographic transition in the past couple of decades. The far-reaching effects of industrialization and urbanization have combined with an increasingly ageing population to create a fertile milieu for the development of chronic NCDs such as diabetes mellitus. At the same

Box 1 | Lessons from the Indian experience with diabetes mellitus

- When individuals and societies rapidly transition from undernutrition to a stage of relative nutritional abundance, huge increases in the prevalence of diabetes mellitus are likely to occur, particularly if the transition is also accompanied by decreases in physical activity levels and a shift to an unhealthy diet in the population
- As the prevalence of diabetes mellitus escalates, the disease will probably affect individuals at younger ages, leaving them prone to developing limb, organ and life-threatening complications. Preventing complications by good control of diabetes mellitus is easier and cheaper than treating such complications once they occur
- Currently, diabetes mellitus in India is mainly confined to more affluent sections of society. However, the disease has begun to develop in the lower socioeconomic strata as well, which has important health implications
- Prevention and control of diabetes mellitus can be achieved by relatively inexpensive means in low-resource settings, such as, by encouraging physical activity and healthier diet options. Judicious use of emerging technologies including telemedicine can help reach remote parts of a developing country.
- Successful containment of the diabetes mellitus epidemic in developing nations requires commitment on the part of all stakeholders in both the governmental and nongovernmental sectors

time, communicable diseases continue to contribute to the overall morbidity and mortality and compete with NCDs for the allocation of scarce health-care resources. This situation is prevalent not only in India, but in other emerging economies of Asia, Latin America and Africa[147,148]. Lessons learned from the history of the diabetes mellitus epidemic in India can, therefore, be used to beneficial effect in these countries as well. Experience gained in managing the disease and its complications in India is also likely to be of immense use to policy makers and health-care providers in countries with large populations of Asian Indian extraction. The salient points learned from the Indian experience with diabetes mellitus over the past four decades are summarized in BOX 1.

Conclusions

Hundreds of millions of individuals in Sub-Saharan Africa, Asia and South America are yet to experience the epidemiological transition from communicable diseases to NCD such as diabetes mellitus. For these populations, the lessons learnt from India's experiences in the fight against diabetes mellitus could be applied with local cultural adaptations. The knowledge we possess, if used appropriately with proper community empowerment, has the potential to slow the epidemic of diabetes mellitus. The dividend, in the form of improved health, productivity and economic development, is well worth the effort.

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Author contributions

R.U. wrote the manuscript. All authors contributed equally to researching data for the article, reviewing and editing the manuscript before submission.

Competing interests statement

The authors declare no competing interests.

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