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OTHER FORMS OF DIABETES AND ITS COMPLICATIONS (JJ NOLAN AND H THABIT, SECTION EDITORS)

Diabetes in South Asians: Phenotype, Clinical Presentation, and Natural History

Ranjit Unnikrishnan [1] · Prasanna Kumar Gupta [1] · Viswanathan Mohan [1]

Abstract

Purpose of Review South Asia is one of the epicenters of the global diabetes pandemic. Diabetes in south Asians has certain peculiar features with respect to its pathophysiology, clinical presentation, and management. This review aims to summarize some of the recent evidence pertaining to the distinct diabetes phenotype in south Asians.

Recent Findings South Asia has high incidence and prevalence rates of diabetes. The progression from "pre-diabetes" to diabetes also occurs faster in this population. Pancreatic beta cell dysfunction seems to be as important as insulin resistance in the pathophysiology of diabetes in south Asians. Recent evidence suggests that the epidemic of diabetes in south Asia is spreading to rural areas and to less affluent sections of society.

Summary Diabetes in south Asians differs significantly from that in white Caucasians, with important implications for prevention, diagnosis, and management.

Keywords Diabetes · Pre-diabetes · South Asians · Phenotype · Incidence · Prevalence

Introduction

The epidemic of type 2 diabetes continues to spread unabated, the latest statistics from the International Diabetes Federation (IDF) estimating the number of individuals affected to be 424.9 million, with an increase to 628.6 million projected by the year 2045 [1•]. These global statistics, alarming in themselves, mask vast inter-regional differences in the diabetes burden worldwide. It is now predicted that the brunt of the diabetes epidemic will fall disproportionately on certain geographical locations, South Asia being the prime example.

In geographical terms, "South Asia" or the "Indian subcontinent" refers to those countries located between the Himalayas to the north and the Indian Ocean to the south. In modern parlance, it comprises the independent nations of India, Pakistan, Bangladesh, Nepal, Bhutan, Sri Lanka, the Maldives, and Mauritius. It accounts for just 11.5% of the world's land area, but it is the most densely populated region in the world, home to 1.7 billion people or more than a quarter of the world's population. Three of the world's most populous countries are located in this region. In addition, there is a large south Asian diaspora across the globe, the numbers of which are estimated to exceed 20 million [2].

It has long been noticed that individuals of south Asian ethnicity have a higher risk of certain non-communicable diseases (cardiovascular disease, dyslipidemia, and most importantly, type 2 diabetes) as compared to white Caucasians [3]. While this propensity was first noted in migrants from south

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✉ Viswanathan Mohan
drmohans@diabetes.ind.in; https://www.drmohansdiabetes.com; https://www.mdrf.in

Ranjit Unnikrishnan
drranjit@drmohans.com

Prasanna Kumar Gupta
drgupta@drmohans.com

[1] Department of Diabetology, Dr. Mohan's Diabetes Specialities Centre & Madras Diabetes Research Foundation, ICMR Centre for Advanced Research on Diabetes, WHO Collaborating Centre, Non-Communicable Disease Prevention & Control & IDF Centre of Excellence in Diabetes Care, No 4, Conran Smith Road, Gopalapuram, Chennai 600 086, India

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Asia to western nations, current evidence shows that it holds good even for native south Asians in their home countries. The exact reasons for this excess risk for diabetes have not been elucidated yet. In addition, type 2 diabetes (T2D) in south Asians exhibits several unique features, which make its diagnosis and management challenging. As the south Asian diaspora expands, clinicians all over the world will need to be aware of the peculiar features of T2D in this ethnic group, so as to offer the best possible care to their patients. In this article, we will review some of the unique features of diabetes in south Asians with respect to its pathophysiology, natural history, and clinical presentation.

Magnitude of the Problem

The International Diabetes Atlas, published by the IDF and now in its eighth edition, is the primary source of information about the diabetes burden faced by regions and countries across the world [1]. As per the Atlas, all nations in south Asia (except Pakistan) are grouped under the South-East Asia (SEA) Region, while Pakistan is listed under the Middle East-North Africa (MENA) region.

The SEA region has the second largest number of people with diabetes in the world (151.4 million), only lagging behind the Western Pacific region, which includes China, the most populous nation in the world. Among the individual nations in south Asia, India has the largest number of people with diabetes (72.9 million) closely followed by Pakistan (7.5 million) [1]. In terms of prevalence, Mauritius ranks first in the region, followed by Sri Lanka and India.

It should, however, be noted that the statistics for most countries in the region (and indeed, for most of the world) are not derived from representative population-based studies, on account of the paucity of such studies from most countries. In India, the nationwide Indian Council of Medical Research—India Diabetes (ICMR-INDIAB) study has provided robust population-based estimates of the diabetes burden in the country [4]. An important finding from the ICMR-INDIAB study is the marked heterogeneity in diabetes prevalence between different states and regions of India, as well as between urban and rural areas ([5 ••]). Such differences are likely to exist in other countries of the region as well, but representative data are scarce.

In addition to high prevalence, the incidence rates of T2D are also higher in south Asians compared to other ethnic groups. In a population-based study conducted in urban adults in southern India, the incidence rate of diabetes was found to be 22.2 per 1000 person-years, which is one of the highest reported worldwide and next only to those reported in Pima Indians [6]. The progression from "pre-diabetes" to diabetes has also been found to occur faster in this population.

A Unique Pathophysiology?

T2D is a heterogeneous entity, spanning the whole spectrum of pathophysiology from a predominant insulin-resistant state to predominant beta cell failure. The peculiar features of "south Asian" T2D have interested researchers for decades and these are summarized in Fig. 1. However, the exact reasons underlying the differences in pathophysiology and clinical presentation remain elusive.

The earliest studies on T2D in south Asians focused on the role of insulin resistance as the primary driver for dysglycemia [7,8]. The concept of the "Asian Indian phenotype" was developed as a corollary to these studies. In a nutshell, the "Asian Indian phenotype" refers to a situation where, for any given level of body mass index (BMI), south Asians have greater total body fat, more visceral fat, more insulin resistance, and a greater propensity to T2D as compared to white Caucasians [3]. It has been suggested that south Asians, while anthropometrically thin, are metabolically obese (the "thin fat Indian"), and this is evident even from infancy [9]. Excess of visceral and hepatic fat, in association with the perturbations in adipokine and lipid levels, is postulated to lead to insulin resistance and compensatory hyperinsulinemia from an early age in this population. Indeed, studies have shown that south Asian infants have higher level of insulin their cord blood compared to Caucasian babies, suggesting that insulin resistance is present even at birth in this population [10].

However, it should be noted that even in the face of extreme insulin resistance, T2D does not develop unless some degree of beta cell dysfunction is present. Recent studies have focused on the role of insulin secretory defects in the pathophysiology of diabetes in south Asians. Compared to populations with high levels of insulin resistance (e.g., Pima Indians), south Asians have been shown to exhibit poorer insulin secretion at baseline and 30 and 120 min following an oral glucose load ([11 ••]).

It has also been suggested that beta cell function declines relatively early among south Asians with dysglycemia. In a cross-sectional study of south Asian adults, beta cell dysfunction was noted even in persons with pre-diabetes irrespective of age, adiposity, family history, and insulin sensitivity [12]. In both native south Asians as well as migrants residing in the USA, beta cell dysfunction was more strongly associated with pre-diabetes and T2D [13, 14]. Studies from the UK have shown that while south Asians tend to have avid insulin secretory responses at younger ages (compensating for lower insulin sensitivity and maintaining euglycemia), beta cell function and glycemic control deteriorate rapidly with age, reflecting exhaustion of their beta cell reserve consequent to exposure to high levels of insulin resistance from a young age [15]. Similarly, studies from the USA have shown that south Asians tend to have poorer beta cell function compared to white Caucasians, African-Americans, Hispanics, and Chinese-Americans [16].

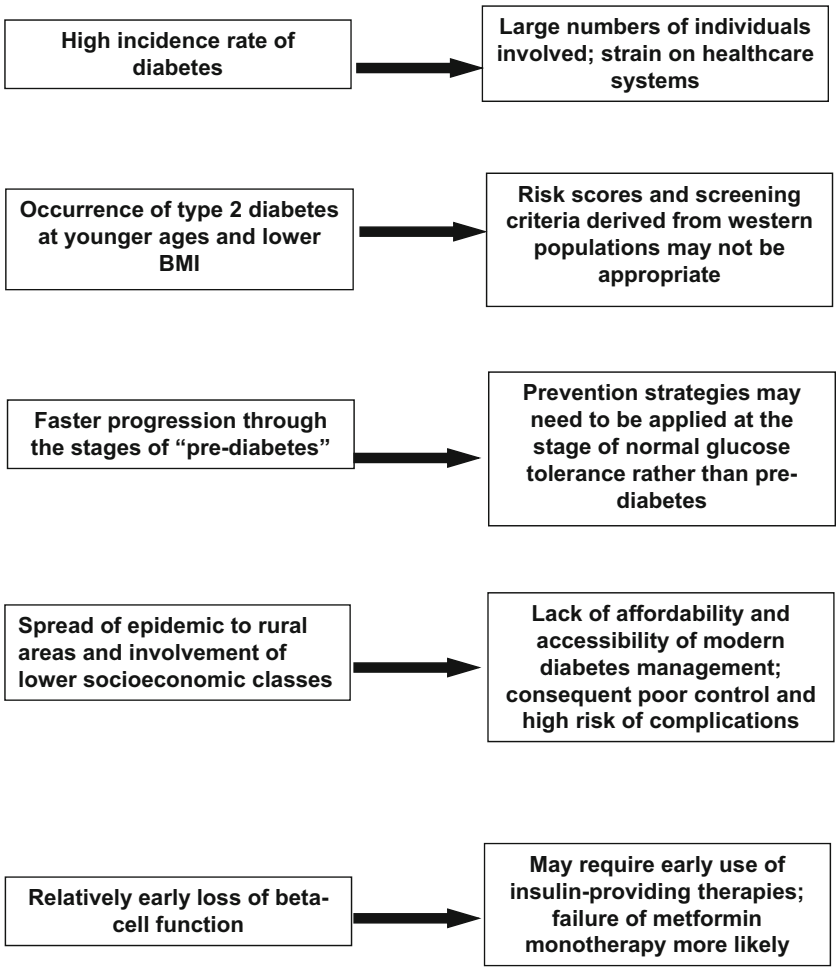

Fig. 1 Clinical implications of the "south Asian phenotype" of type 2 diabetes

The reasons for poor beta cell reserve in south Asians are still not clear. There has been considerable interest in the role of intrauterine malnutrition in pancreatic development and function, but most data have linked the intrauterine environment to insulin resistance rather than insulin secretory defect [17]. However, in a study from Denmark, low birth weight was found to be associated with reduction in β cell function in middle age [18]. It is now thought that an adverse intrauterine environment is likely to be one of the factors underlying beta cell dysfunction in south Asians and that the subsequent deterioration of insulin secretory responses and glycemic control is exacerbated by insulin resistance. Beta cell dysfunction may also arise as a result of genetic and epigenetic influences or endocrine disruptors such as pollutants, but it is premature to attribute major roles to these factors at present [19].

Other Forms of Diabetes in South Asians

While T2D constitutes more than 90% of all cases of diabetes in the south Asian region (as elsewhere in the world), other forms of diabetes are also not infrequent in this population. Populations of non-Caucasian origin have traditionally been considered to have a low risk of type 1 diabetes (T1D); however, it should be noted that south Asians have a higher incidence of T1D than either Africans or Chinese [1]. The total number of children and adolescents living with T1D in the South-East Asian region is estimated to be 149,300. There is some evidence that the genetic factors conferring risk of T1D are different in south Asians compared to Europeans [20]. It has also been noted that a significant proportion of south Asian patients with T1D test negative for pancreatic autoantibodies [21], raising the possibility of misclassification.

Fibrocalculous pancreatic diabetes (FCPD) is a unique form of secondary diabetes occurring as a consequence of non-alcoholic chronic calcific pancreatitis. Its prevalence is confined to tropical regions of the world. Specifically, in south Asia, it is most frequent in the states of Kerala and Tamil Nadu in southern India. Patients present with recurrent abdominal pain in childhood, features of exocrine pancreatic insufficiency in adolescence and insulin-requiring diabetes in early adulthood. Plain abdominal radiograph will show pancreatic calcification and is the investigation of choice. The exact etiology is unknown, but the incidence has been declining in recent years [22].

Recently, there has also been considerable interest in the monogenic forms of diabetes (including maturity onset diabetes of the young (MODY) and neonatal diabetes). There is little data from south Asia on the prevalence of these syndromes, but studies in the migrant south Asian population in the UK suggest that the prevalence may be lower than in White Caucasians [23]. A few clinic-based studies from southern India have shown that genetic mutations were present in only around 10% of patients suspected to have monogenic diabetes by clinical criteria [24–26]. Lack of awareness among patients and clinicians and the high cost and unavailability of genetic testing (the gold standard for diagnosis) are major stumbling blocks in the wider recognition of these monogenic forms of diabetes.

In parallel with the increasing prevalence of T2D in south Asians, gestational diabetes mellitus (GDM) has also become more common in this population. The prevalence of GDM in India, which was only around 2% in the 1980s, has rapidly increased to almost 20% in some urban areas [27]. With the onset of T2D shifting to younger ages, clinicians are also increasingly likely to encounter women with pre-gestational (pre-existing) T2D complicating pregnancy in this ethnic group. In a study from Sri Lanka, the ratio of pre-gestational to gestational diabetes among women attending antenatal clinic was found to be 1:4, a much higher figure than reported among Caucasian populations [28]. Similarly, a Norwegian study found that the prevalence of pre-gestational diabetes was twice as high in immigrants from south Asia as compared to the native population [29].

Changing Face of Type 2 Diabetes in South Asians

Parallel to the explosive increase in the prevalence of T2D in south Asia, the clinical presentation of the disease has also undergone a sea change. T2D has traditionally been considered a disease of middle to older age groups and has been noted to disproportionately affect individuals residing in urban areas and belonging to the higher socioeconomic strata of the population. All these assumptions are now being challenged by recent findings.

Studies over the past three decades have clearly shown that south Asians develop T2D at least a decade earlier than White Caucasians [30]. Similarly, in the ICMR-INDIAB study, the take-off point for the prevalence of diabetes was 25 to 34 years [31]. Earlier onset of disease implies longer exposure to hyperglycemia and the likelihood of development of debilitating and even life-threatening complications during middle age, which constitutes the prime of most individuals' productive lives. With progressive increases in pediatric obesity and BMI, childhood onset T2D has also started making its appearance in these countries [32].

The prevalence of diabetes in urban areas of south Asia still significantly exceeds that in rural areas. However, there have been rapid increases in diabetes prevalence in the rural parts of these countries as well in recent years. As most of the population of these countries resides in rural areas, even a small increase in the rural prevalence of diabetes will translate into a huge increase in the diabetes burden borne by the country. Also, on account of lower levels of education and lack of affordable and accessible health care, rural dwellers may be less able to care for their diabetes than their urban counterparts, placing them at greater risk for complications.

The most worrying aspect of the changing face of the diabetes epidemic in south Asia is its spread to the economically disadvantaged sections of society. In 2001, a study conducted in two economically disparate residential areas of Chennai City in southern India showed that the prevalence of diabetes in the more prosperous locality was twice that in the less prosperous locality; by 2011, this difference was shown to have been all but obliterated [33]. In the ICMR-INDIAB study, it was shown that in urban areas of those states of India with high prevalence of diabetes, the prevalence was higher among individuals of lower socioeconomic status than in the more prosperous sections of society, clearly indicating that the epidemic is spreading to those individuals who can least afford to pay for its management [5].

Migrants from south Asia to western countries have long been considered to be at high risk for diabetes. Throughout the 1980s and 1990s, the prevalence of diabetes in these migrant communities remained far higher than in the native south Asian population. However, recent evidence suggests that the pattern has reversed and native south Asians in some locations now have a higher prevalence of diabetes than migrants [34]. This indicates that the epidemic of T2D has well and truly come to stay in south Asia, with significant implications for the young and growing population of this region.

Complications of Diabetes in South Asians

Much of the morbidity and mortality due to diabetes can be attributed to its chronic complications. There is some evidence to show that there are ethnic differences in susceptibility to various diabetic complications. Studies in migrant south Asian populations in the 1980s supported the notion that these individuals were more prone to microvascular complications, particularly nephropathy, as compared to White Caucasians. However, recent studies on the native south Asian population have failed to confirm this. Indeed, there is some evidence that the prevalence of diabetic retinopathy and nephropathy might be lower in south Asians with diabetes, compared to the figures reported for other ethnic groups [35,36]. Similarly, a

study from the UK suggested that individuals of south Asian ancestry had lower prevalence of diabetic neuropathy compared to White Caucasians; however, subsequent studies have failed to confirm this [37,38].

South Asians are considered to be a high-risk group for the development of atherosclerotic cardiovascular disease and the coexistence of diabetes likely worsens the risk [39]. South Asians, even in the absence of diabetes, tend to have an atherogenic lipid profile, characterized by low levels of high-density lipoprotein (HDL) and high levels of triglycerides. Even after adjusting for age, gender, smoking status, hypertension, and obesity, migrant south Asians with diabetes are three to four times more likely to develop ASCVD than their white Caucasian counterparts [40]. However, there is little data on the excess risk of ASCVD conferred by diabetes among native Asian Indians.

Clinical and Policy Implications

The unique features of diabetes in south Asians described earlier have important implications with respect to the diagnosis, prevention, and management of the disease.

Global guidelines on screening for T2D focus on "at risk" groups such as individuals with high BMI, family history of diabetes, or prior diagnosis of pre-diabetes [41]. These criteria may not hold good in the south Asian population for reasons already mentioned. Therefore, most guidelines now recommend universal screening for T2D in the south Asian population, starting at earlier ages. While universal screening would be ideal, cost and logistic constraints limit its use in most countries of this region. Identifying "extreme high-risk" individuals in the population using validated risk scores such as the Indian Diabetes Risk Score (IDRS) (Table 1) represents a feasible means of diabetes screening in this region [42].

Several large randomized trials have demonstrated the feasibility of preventing T2D in individuals with pre-diabetes, by means of lifestyle modification, drugs, or a combination of the two [43–45]. However, in the Indian Diabetes Prevention Program, the magnitude of reduction in diabetes incidence in the intervention arms (both lifestyle modification and metformin) was significantly lower than in the U.S. Diabetes Prevention Program, which utilized the same methodology [46]. It is possible that earlier development of beta cell dysfunction in the south Asian

Table 1 Indian Diabetes Risk Score (IDRS)

Particulars	Score
Age	
< 35 years	0
35–49 years	20
≥ 50 years	30
Waist circumference	
Waist < 80 cm (female), < 90 cm (male)	0
Waist ≥ 80–89 cm (female), ≥ 90–99 cm (male)	10
Waist ≥ 90 cm (female), ≥ 100 cm (male)	20
Physical activity	
Vigorous exercise (regular) or strenuous (manual) work at home/work	0
Moderate exercise (regular) or moderate physical activity at home/work	10
Mild exercise (regular) or mild physical activity at home/work	20
No exercise and sedentary activities at home/work	30
Family history of diabetes	
No diabetes in parents	0
One parent has diabetes	10
Both parents have diabetes	20

If the score is …

≥ 60: Very HIGH RISK of having diabetes. Oral glucose tolerance test is recommended to rule out diabetes. If this is not possible, at least a random blood sugar or a fasting blood sugar should be done

30–50: The risk of having diabetes is MODERATE . It is still recommended to have the above checkup

< 30: Risk of having diabetes is probably LOW

Note: The Indian Diabetes Risk Score applies only to type 2 diabetes. People with other forms of diabetes need not have high-risk score

(Reproduced with permission from: Indian J Endocrinol Metab. 2013;17:31–36) [42]

population renders them less responsive to the benefits of lifestyle modification and metformin, both of which work by improving insulin sensitivity with minimal effects on beta cell function [11]. This is particularly so in individuals with isolated impaired fasting glucose (IFG), where the primary defect lies in early phase insulin secretion [47]. Also, as south Asians tend to progress rapidly from normoglycemia to T2D, targeting prevention strategies to individuals with pre-diabetes may be too late [6]. For the best results, lifestyle modification should be directed at individuals at high risk for diabetes (e.g., as defined by the IDRS) even if they are currently normoglycemic.

As a corollary, there is also some evidence to show that south Asians respond better to insulin-providing antidiabetic therapies than insulin sensitizing agents, compared to other ethnic groups. In a multinational trial evaluating the efficacy of the dipeptidyl peptidase-4 (DPP-4) inhibitor sitagliptin as monotherapy for T2D, the greatest glycated hemoglobin (HbA1c) reductions were found in Indian patients as compared to Koreans and Chinese [48]. However, these findings need to be confirmed by larger trials; also, it is not clear whether this finding holds good for other insulin secretagogues such as sulfonylureas, meglitinide analogues, or other DPP-4 inhibitors.

Conclusions

South Asia faces a double burden of disease, with communicable diseases still accounting for much morbidity and mortality, while non-communicable diseases such as diabetes are gaining ground as accompaniments of economic progress and urbanization. The diabetes epidemic in south Asia affects, directly or indirectly, more than a fourth of humanity. The societal and economic costs of the disease and its complications are correspondingly immense. Research over the past several decades has uncovered a great deal of information about the nature of diabetes in south Asians and its peculiar features. While much remains to be learned, the immediate challenge is to translate current knowledge into action and ensure that the epidemic is halted in its tracks or at least slowed down, so that south Asia will be spared of the epithet "Diabetes Capital of the World."

Compliance with Ethical Standards

Conflict of Interest Ranjit Unnikrishnan, Prasanna Kumar Gupta, and Viswanathan Mohan declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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