Review Article

Why Are Indians More Prone to Diabetes?

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Abstract

Diabetes, a global public health problem, is now emerging as a pandemic and by the year 2025, three-quarters of the world's 300 million adults with diabetes will be in non-industrialized countries and almost a third in India and China alone. There is evidence from several studies that the prevalence of Type 2 diabetes is increasing in migrant Indians. Today, the prevalence of diabetes in the urban metros of India is approaching the figures reported in the affluent migrant Indians. Environmental and lifestyle changes resulting from industrialization and migration to urban environment from rural settings may be responsible to a large extent, for this epidemic of Type 2 diabetes in Indians. Obesity, especially central obesity and increased visceral fat due to physical inactivity, and consumption of a high-calorie/high-fat and high sugar diets are major contributing factors. There is also strong evidence that Indians have a greater degree of insulin resistance and a stronger genetic predisposition to diabetes. As several of the factors associated with diabetes are potentially modifiable, this epidemic of diabetes can be curbed if proper measures are taken to increase physical activity and reduce obesity rates in adults, and most importantly, in children. In addition, strategies to achieve healthy fetal and infant growth and encouraging the use of traditional diets rich in fibre are also important steps. Such interventions should be attempted in those who are genetically predisposed to diabetes in order to tackle the explosion of, and thereby reduce the burden due to, diabetes within the Indian subcontinent. ©

Magnitude Of The Problem Of Diabetes In India

Diabetes poses a major health problem globally and is one of the top five leading causes of death in most developed countries. A substantial body of evidence suggests that it could reach epidemic proportions particularly in developing and newly industrialized countries.[1] Indeed, by the year 2025, three-quarters of the world's 300 million adults with diabetes will be in developing countries, and almost a third in India and China alone.[2] The prevalence of diabetes in India is showing a sharp upswing as is evident from secular trends from different parts of the subcontinent and studies of migrant Indians.[3] The World Health Organization has estimated that in 1995,19.4 million individuals were affected by diabetes in India and these numbers are expected to increase to 57.2 million by the year 2025 i.e. one-sixth of the world total.[1] The revised figures are 80.9 million by the year 2030.[4] This article will focus on the possible reasons why this epidemic of diabetes is occurring in Indians.

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Recent epidemiological studies have reported that migrant Asian Indians living in different parts of the world show a much higher prevalence of diabetes than the host populations of those countries.[5-7] This was attributed to changes in environmental factors, such as increased affluence, which unmask an increased genetic or ethnic propensity for diabetes.[7] Studies have revealed that migrant Indian populations irrespective of differences in anthropometry, dietary and socio-economic factors and migratory patterns, had a higher prevalence of Type 2 diabetes than Europeans.[8] Joshi [9] has described a typical Asian Indian phenotype with higher percentage of body fat and increased waist to hip ratio for any given body mass index (BMI) which predisposes to diabetes and the metabolic syndrome.

Recent trends indicate that even within the Indian subcontinent, the prevalence of diabetes is rising in astronomical proportions. In the early 1970's, the prevalence of diabetes among urban Indians was reported to be 2.1% which has steadily risen to figures now ranging between 12-16 % as summarized in Table 1.[10-17] Looking at the region-wise prevalence of diabetes, in a recent study conducted among urban subjects [National Urban Diabetes Survey (NUDS)] the prevalence of diabetes in the southern part of India was found to be higher -13.5% among Chennai residents, in Bangalore, 12.4% and Hyderabad,16.6% than

eastern India, 11.7% (Kolkatta), northern India, 11.6% (New Delhi) and western India, 9.3% (Mumbai).[12] Thus it is clear that in the last two decades, there has been a marked increase in the prevalence of diabetes among urban Indians, with a suggestion that Southern India has seen the sharpest increase. Although in rural India the prevalence of diabetes is much lower than in the urban population,[18] even here the prevalence rates are rapidly rising, though clearly more studies are needed.

Increasing prevalence of Type 2 diabetes in children, teenagers and adolescents is a new and alarming facet of the epidemic of diabetes in USA and Japan.[19,20] Although, there are few data on Type 2 diabetes in children and adolescents in India, it is reasonable to believe that this is a phenomenon waiting to declare itself in a large measure in India also. Indeed, the rising prevalence of Type 2 diabetes in children is a reflection of the effects of globalization and industrialization affecting all societies.[21]

Table 1 : Prevalence of diabetes in urban India

Year	Author	Place	Prevalence (%)
1972	Ahuja *et al*[9]	ICMR Multicentre Study	2.1
1988	Ramachandran *et al*[13]	Kudremukh	5.0
2000	Raman Kutty *et al*[14]	Thiruvananthapuram	12.4
2001	Iyer *et al*[15]	Dombivli	7.5
2001	Misra *et al*[16]	New Delhi	10.3
2001	Mohan *et al*[11]	Chennai	12.0
2001	Ramachandran *et al*[12]	National Urban Diabetes Survey(Six Cities)	12.1 (9.3 -16.6)
2002	Gupta *et al*[17]	Jaipur	12.7

Reasons For Escalation In Diabetes Prevalence In India

Despite the diversity within India, a number of common themes can be found with regard to patterns of diabetes and rising prevalence rates. The reasons for the escalation in diabetes in Indians are i) increased insulin resistance, ii) stronger genetic factors and iii) environmental factors particularly associated with urbanization.

i) Increased Insulin resistance

One of the important factors contributing to increased Type 2 diabetes in Asian Indians is the fact that they have a greater degree of insulin resistance compared to Caucasians.[22,23] Mohan *et al*[24] first demonstrated that Asian Indians have higher insulin levels to a glucose load than Europeans (hyperinsulinemia). It was later demonstrated by euglycaemic clamp studies that insulin resistance is greater among Asian Indians compared to age, sex and body mass index matched Europeans.[25] This has subsequently been confirmed by several studies.[22,26,27]

Studies by Yajnik *et al*[28,29] demonstrated that low birth weight is a contributor to insulin resistance among Indians. His group also showed that Indian neonates have higher insulin levels and greater adiposity even at birth compared to Caucasians.[30] The hypothesis is that small Indian babies have smaller abdominal viscera and low muscle mass, but preserve body fat during their intrauterine development, which may predispose to an insulin-resistant state.[31] He also suggested that accelerated childhood growth may be a risk factor for adiposity and insulin resistance, especially in children with low birth weight and that childhood growth seems to be more influenced by paternal genetic factors, whereas intrauterine growth is more influenced by intrauterine environment.[32] A recent long term follow up study supports this hypothesis and shows that lower birth weight coupled with obesity in childhood and adolescence leads to very high rates of diabetes.[33]

It is now well known that insulin resistance clusters with other components of the metabolic syndrome like abdominal obesity, glucose intolerance/Type 2 diabetes mellitus, dyslipidaemia and hypertension and hence this syndrome is also called the insulin resistance syndrome (IRS). Recent studies in India have reported high prevalence of IRS in the general population, which is higher in urban compared to the rural population.[34-36] We recently reported that the overall prevalence rate of IRS in the Chennai Urban Population Study (CUPS) is 11.2 percent even using conservative definitions like the European Group on Insulin Resistance (EGIR).[37] Moreover the prevalence of IRS in the middle-income group (18.7%) was significantly higher compared to the low income group (6.5%).[34] Age, body mass index, central obesity, cholesterol, triglycerides, physical inactivity and higher socio-economic status positively correlated with IRS in this study.[34] Gupta *et al*[36] reported the overall IRS prevalence to be 12.8% and noted that subjects with diabetes as well as IRS have greater prevalence of obesity, central obesity, hypertension, hypertriglyceridemia and low HDL as compared with normal subjects.

Studies have also shown that migrant Asian Indians have a greater propensity for developing the metabolic syndrome compared to host populations.[22,38,39] The overall prevalence of insulin resistance syndrome was higher in Indians [11.2%][34] compared to other ethnic groups [Mexicans:3.0%, Japanese:1.6%].[40,41] From these studies it can be hypothesized that increased insulin resistance can at least partly explain the high prevalence of diabetes in both native and migrant Indians. Whether this increased insulin resistance is due to genetic or environmental factors is still debatable and the available evidence is summarized below.

ii) Stronger Genetic Factors in Indians

The epidemic increase in diabetes in India along with various studies on migrant and native Indians clearly indicate that Indians have an increased predilection to diabetes which could well be due to a greater genetic predisposition to diabetes in Indians. Genetic susceptibility appears to play an important role in the occurrence of Type 2 diabetes.[42] However, Type 2 diabetes is known to be a multifactorial disease caused by a complex interplay of genetic (inheritance) and environmental (diet and lifestyle) factors[43] that influence a number of intermediate traits of relevance to the diabetic phenotype (e.g., β-cell mass, insulin secretion, insulin action, fat distribution, obesity).[44] The complex interactions between

genes and environment complicate the task of identifying any single genetic susceptibility factor for Type 2 diabetes.

Type 2 diabetes shows a clear familial aggregation but it does not segregate in a classical Mendelian fashion. In western populations it has been demonstrated that risk for Type 2 diabetes among offspring with a single diabetic parent was 3.5-fold higher and for those with two diabetic parents was 6-fold higher compared with offspring without parental diabetes.[45] A strong familial aggregation of diabetes is observed among Asian Indians, with high prevalence among the first-degree relatives and vertical transmission through two or more generations. Comparative studies on migrant Indians and Europeans conducted in U.K by Mohan *et al.*[46] in the 1980's showed, that 10% of Asian Indian diabetic patients had both parents with diabetes, compared to only 1% of European diabetic patients.

In a study conducted by Viswanathan *et al*,[47] to determine the prevalence of Type 2 diabetes in offspring of two diabetic parents, diabetes was observed in 50% of offspring, while 12% had impaired glucose tolerance(IGT). Thus sixty two percent of all South Indian offspring of two diabetic parents had abnormal glucose tolerance which is considerably higher compared to figures around 25% among Europeans.[47] This might represent an ethnic variation of the genetic factors operating in Indian patients predisposing to Type 2 diabetes.

Diabetes also develops at a younger age in Indians, i.e., at least a decade or two earlier than Europeans.[11,48] Maturity onset diabetes of the young (MODY), a monogenic form of diabetes, is characterized by an autosomal dominant inheritance, age of onset at 25 years or younger, absence of ketosis and response to oral agents. It has been estimated that 2-5% of all patients with Type 2 diabetes may have MODY forms of diabetes. Earlier studies by Mohan *et al*[49] reported on the high prevalence of MODY (using the clinical criteria used at that time) in South Indians. He also reported on the insulin responses in MODY[50] and the beta-cell response in the offspring of MODY.[51] These studies indicated that insulin resistance was more pronounced in MODY compared to classical older onset Indian Type 2 diabetic subjects.[49,50] Further studies are needed in India to determine what percent of youth onset diabetes have MODY and what percent have early onset Type 2 diabetes. This can be assessed by looking at the MODY genes in our population.

In the Chennai Urban Population Study (CUPS), the prevalence of diabetes was higher among subjects who had positive family history of diabetes (18.2%) compared to subjects without a family history of diabetes(10.6%). The overall prevalence of glucose intolerance (Diabetes + IGT) among subjects with two diabetic parents was significantly higher (55%) than those who had one diabetic parent (22.1%) or those with two non-diabetic patients (15.6%).[52] Several studies clearly demonstrate that "Double Gene Dose Effect" (both parents diabetic) is high among Indians (Fig. 1).[45,47,53]

Despite all the evidence for stronger genetic factors operating in Indians given that the population gene pool shift occurs very slowly, it is more likely that the current

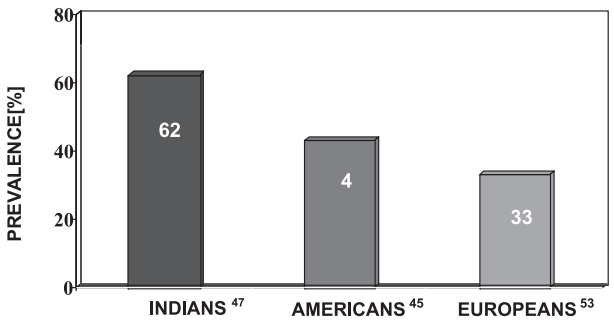

Fig. I : Prevalence of abnormal glucose intolerance in offspring of conjugal diabetic parents (OCDP)

epidemic of diabetes is reflective of rapid lifestyle changes i.e., is the effect of environmental changes rather than due to genetic factors. However, it is necessary to take up large scale genomic studies on diabetes in Indians to see whether any peculiar set of genes predisposes to diabetes in Indians.

iii) Role of Environmental Factors

Epidemiological Transition

Currently, India is undergoing a rapid epidemiological transition with increased urbanization. The current urbanization rate is 35% compared to 15% in the 1950's and this could have major implications on the present and future disease patterns in India with particular reference to diabetes and coronary artery disease.[1,55] Socio-economic development over the last 40-50 years has resulted in a dramatic change in lifestyle from traditional to modern, leading to physical inactivity due to technological advancement, affluence leading to consumption of diets rich in fat, sugar and calories and a high level of mental stress. All these could adversely influence insulin sensitivity and lead to obesity. Since 1970, several studies have been done comparing urban and rural populations in India, which have shown higher prevalence of diabetes among urban residents compared to their rural counterparts both in southern and northern parts of India.[9,55-57]

As there is marked variation in living conditions even within the urban area. In order to assess the effect of urbanization and socioeconomic factors on the prevalence of diabetes in India, a population-based study was taken up in urban South Indians called the Chennai Urban Population Study (CUPS) involving two residential areas representing the lower and middle income group involving 1262 participants.[10] 12.4% of the middle income group in Chennai had diabetes against 6.5% in the lower socio-economic group which clearly demonstrates that with affluence, there is a marked increase in the prevalence rates of diabetes even within the urban setting.[10] Other studies also have confirmed that the prevalence of diabetes in India was lower among those with a low income than among more affluent groups.[58]

Physical Inactivity

There are ample epidemiological evidences to demonstrate that physical inactivity as an independent risk factor is fuelling the epidemic of Type 2 diabetes, predominantly in the urban

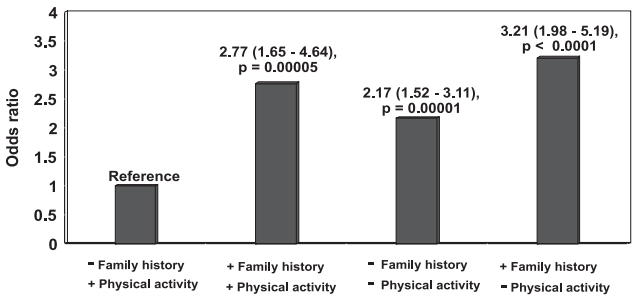

Fig. 2 : Interaction of genetic and lifestyle factors on diabetes.[52]

areas. One of the important reasons for the low prevalence of diabetes in the Indian rural-based population could be that these individuals have a physically vigorous lifestyle. In his study Misra *et al*[16,59] reported that migration from rural areas to urban slums in metropolitan cities leads to obesity, glucose intolerance and dyslipidemia. Adaptation of western lifestyle with increasing physical inactivity could be an important contributor to these factors. In Fiji, among Melanesian and Indian men, the prevalence of diabetes was more than twice as high in those graded as sedentary or undertaking light activity as in those classified as performing moderate or heavy exercise.[60]

In the CUPS participants, prevalence of diabetes was significantly higher among the subjects with light grade activity (17%) compared to moderate grade (9.7%) and heavy grade activity (5.6%). The risk of developing diabetes in the subjects who followed a sedentary lifestyle was three times higher compared to the more physically active.[52] The participants belonging to high socioeconomic status(SES) and who had a positive family history of diabetes had five times greater prevalence of glucose intolerance compared to participants from lower SES and no family history. Thus the CUPS clearly demonstrated that positive family history and lifestyle factors like physical inactivity and high SES have a synergistic effect in the development of diabetes (Fig. 2).[52] It is thus clear that a combination of genetic and environmental factors contribute to diabetes. The increased prevalence of obesity in the urban adolescents, a factor responsible for development of diabetes could also be due to sedentary activity.[61]

Obesity

The role of obesity in the pathogenesis of Type 2 diabetes is complex and is confounded by many heterogeneous factors. Indeed, the intimate relationship between diabetes and obesity has given rise to the term "diabesity" to characterize the close association of these two disorders.[62] Chan *et al*[63] have demonstrated that the relative risk of Type 2 diabetes increases as body mass index (BMI) increases in the US population . In his study men with a BMI of > or = 35 kg/m^2 had a multivariate RR of 42.1 for of Type 2 diabetes compared with men with a BMI < 23.0 kg/m^2. CUPS also revealed that proportion of obesity was significantly higher among those with impaired glucose tolerance(diabetes+IGT) compared to those with normal glucose tolerance (54.1% vs 23.6%) and the similar trend was observed in the proportion of abdominal obesity (62.2% vs 23.5%).[52] Furthermore, Chandalia *et al*[22] have shown that for any BMI, migrant Indians had higher body fat and for any given body fat, they also had higher insulin resistance compared to other ethnic groups independent of generalized or truncal adiposity.

The results of a recent study conducted in North India[64] indicated that there was a strikingly high prevalence of abdominal obesity and generalized obesity as determined by body fat percentage in type 2 diabetic individuals. Another study by Singh *et al*[57] showed that overweight/obesity and central obesity were significantly associated with diabetes. Obesity has been on the increase in the children, which might play a causative role in the escalating prevalence of diabetes in the young.[65,66] This increased occurrence of overweight in childhood, may be the first sign of insulin resistance and future metabolic syndrome. A study conducted in affluent adolescent school children in Delhi has highlighted that obesity is an emerging health problem in adolescent children belonging to affluent families (7.4%) with the maximum prevalence found during the pubertal period(10-12 years).[67]

Bhargava *et al*[33] studied the incidence of IGT and type 2 diabetes in young Indian adults (26 to 32 years of age) whose growth has been recorded prospectively since birth. It was concluded that there was an association between thinness in infancy and the presence of IGT or diabetes in young adulthood and progress to higher categories of body-mass index after the age of two years. Fall *et al*[68] speculate that the increase in Type 2 diabetes in Indian urban populations may have been triggered by mild obesity in mothers, leading to glucose intolerance during pregnancy, macrosomic changes in the fetus, and insulin deficiency in adult life.

Dietary alterations

In India, as urbanization and economic growth occurs, there are major deviations in the dietary pattern which are influenced by the varied cultural and social customs. Traditional dietary patterns are disappearing as Indians are adapting themselves to living in the more industrialized, urban environments that are brought about by globalization. The major dietary changes that urbanization and affluence bring about are, substitution of unrefined wheat, rice or millets by highly polished wheat or rice and increased intakes of fat in higher income groups. High calorie intakes by high-income groups in India are largely due to high intakes of refined cereals and carbohydrates rather than fats and meat as in Europe and North America.[69]

A high intake of saturated fatty acids has been associated with increased risk of developing impaired glucose tolerance (IGT) and diabetes and of progression to diabetes from IGT, whereas unsaturated fatty acids, especially n-3 polyunsaturated fatty acids, have been inversely associated with risk of diabetes.[70] In India not many epidemiological surveys have been able to show an independent association of dietary principles with increasing prevalence of diabetes, however studies conducted in western populations[71,72] have

indicated that higher consumption of whole grain products and exchanging unsaturated fat for saturated fat may reduce the risk for type 2 diabetes and impaired glucose tolerance. In the CUPS study[10] the dietary profile of the middle income group showed higher intake of calories, total fat, saturated fat and sugar compared to low income group substantiating the fact that dietary pattern may be responsible for higher diabetes prevalence rates among the middle income group compared to their lower income group counterparts.

Conclusions

It is thus clear that the diabetes epidemic experienced in India may be due to strong genetic factors coupled with urbanization and lifestyle changes leading to insulin resistance. The contributing factor for increased insulin resistance may be the Asian Indian phenotype consisting of higher rates of central obesity and increased visceral fat. Sufficient evidence is now available to show that many of the environmental factors adversely related to glucose intolerance are modifiable through lifestyle changes.[73-75] Prevention of Type 2 diabetes will require measures to promote physical activity and reduce obesity in adults and children, alongside programmes to achieve healthy fetal and infant growth. Considering that Indians appear to be generally more insulin resistant, it would be prudent to advise a healthy lifestyle across the different geographic regions and age groups, continue traditional diets rich in fibre and possibly adopt stress reduction measures by yoga or other measures. Such an effort is urgently needed to tackle the explosion of diabetes and lower the burden due to the disease in India.

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