International Journal of Diabetes in Developing Countries (January–March 2019) 39(1):8–14
https://doi.org/10.1007/s13410-018-0630-5

REVIEW ARTICLE

The ongoing epidemic of diabetes mellitus in India: genetics or lifestyle?

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Received: 13 September 2017 / Accepted: 29 March 2018 / Published online: 13 April 2018

Abstract
India is estimated to have the second highest number of cases of diabetes mellitus in the world after China. Recent epidemiological evidence indicates that people of lower socioeconomic group in India are equally or even more susceptible to diabetes. Family history is a very strong risk factor for developing type 2 diabetes mellitus; the lifetime risk is nearly 40% for individuals who have one parent affected and approaches 70% if both parents are affected. Genome-wide association studies identified more than 50 genetic variants associated with type 2 diabetes mellitus, but these risk alleles identified to date could only explain less than 10% of the observed heritability. Acquisition of the same unhealthy lifestyle from the parents could be the major reason for the observed heritability that genetics could not explain. The global age-standardised prevalence of diabetes has nearly doubled since 1980, rising from 4.7 to 8.5% in the adult population. If genes are responsible for this doubling of prevalence, the responsible gene pool should also amplify to the same extent in the population. The Hardy–Weinberg law states that allele and genotype frequencies in a population will remain constant from generation to generation in the absence of other evolutionary influences, making genetics as the etiology for this ongoing epidemic less likely. Indians have a tendency to become metabolically obese and develop type 2 diabetes mellitus with normal weight; thus, body mass index cut-off for overweight and obesity is kept lower in Indians. Primary and secondary prevention strategies should be more emphasised at the community level. Physical activity recommended is at least 150 min/week. All adults should decrease the amount of time spent in daily sedentary behaviour. Dietary modifications by reducing carbohydrate intake and increasing the intake of proteins, green leafy vegetables, fruits, and nuts should be promoted.

Keywords Diabetes mellitus · Heritability of diabetes · Lifestyle · Thin fat Indian · Central obesity

Introduction

India is home for 69.2 million people living with diabetes mellitus (DM) and is estimated to have the second highest number of cases of DM in the world after China as per the 2015 data [1]. Though historically a disease of the affluent, recent epidemiological evidence indicates that people of lower socioeconomic group in India are equally or even more susceptible to type 2 diabetes mellitus (T2DM) [2]. DM represents one of the most serious threats to India's public health in the twenty-first century in terms of health and economic tolls, considering the projected increase in prevalence and increasing incidence at younger age. A targeted approach to prevention may be the best tool to curtail the growth of this diabetic epidemic.

Family history in type 2 diabetes mellitus

Family history is a very strong risk factor for developing T2DM; the lifetime risk is nearly 40% for individuals who have one parent with T2DM and approaches 70% if both parents are affected [3–5]. Concordance rate of T2DM in monozygotic twins is about 70% and in dizygotic twins is 20–30% [6]. Prospective studies have demonstrated that family history in a first-degree relative is associated with a twofold increase in the risk of future T2DM [7, 8].

Genetic basis

The strong familial association observed in T2DM is the reason to suggest a genetic basis for the aetiology. The ability to

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interrogate the entire genome was made possible by two key advances, the completion of the Human Genome project and the International HapMap project [9–12]. Genome-wide association studies (GWAS) have identified more than 50 genetic variants associated with T2DM to date, but these risk alleles could only explain less than 10% of the observed heritability of T2DM [13]. GWAS mostly identifies single-nucleotide polymorphisms (SNPs), but there can still be many more relatively uncommon variants associated with diabetes.

Epidemiological data on DM do not support a genetic basis for the current global epidemic. Globally, an estimated 422 million adults were living with diabetes in 2014, compared to 108 million in 1980 [14]. The global prevalence (age-standardised) of diabetes has nearly doubled since 1980, rising from 4.7 to 8.5% in the adult population [14]. In other words, the prevalence of diabetes mellitus has doubled after one generation, i.e. over a span of 35 years. If genes are responsible for this doubling of prevalence, the prevalence of specific alleles responsible for T2DM should also double in the population. The Hardy–Weinberg law states that allele and genotype frequencies in a population will remain constant from generation to generation in the absence of other evolutionary influences. It is therefore unlikely that the gene pool responsible for diabetes doubles after one generation. A genetic basis has also been postulated for the higher prevalence of T2DM among South Asians when compared to Europeans. However, a recent systematic review that compared the risk alleles of SNPs that predispose to T2DM between South Asians and Europeans revealed no substantial difference to indicate that South Asians possess a greater genetic risk [15].

Explanation for the observed heritability

If genes could explain only less than 10% of the observed heritability, then what could be causing the familial preponderance of T2DM? The most plausible explanation is the acquisition of the same unhealthy diet and lifestyle from the parents. Eating behaviours evolve during the early years of life; children learn what, when, and how much to eat through direct experiences with food and by observing the eating behaviours of others. A child's relationship with food is set by the family, and he/she would mimic their diet and lifestyle practices. The child would also be exposed to the metabolic effects of the same from a very early age [16]. Many societies perceive larger infants as healthy and a sign of successful parenting. Therefore, feeding strategies in these societies are designed to increase children's food intake and promote weight gain. However, when these strategies persist in environments with abundance of food, they tend to promote unhealthy diets, accelerated weight gain, and obesity.

Epigenetics is another cause that may contribute to the observed heritability of T2DM. Environment can influence the expression of the genome by methylation of DNA, post-translational modification of histones, and activation of microRNAs. These modifications in DNA can be transmitted through the germline, producing a phenotypical change that is heritable. The unfavourable metabolic milieu as a consequence of bad diet and lifestyle can thus be transferred to the next generation by epigenetics [16]. A nested case-control study of DNA methylation among 25,372 participants in the London Life Sciences Prospective Population (LOLIPOP) found a 2.5 times higher T2DM incidence among Indian Asians than Europeans after 8-year follow-up, even after adjustment for adiposity, physical activity, family history of type 2 diabetes, and baseline glycemic measures. Using epigenome-wide association analyses, DNA methylation markers at five loci were found to be associated with future type 2 diabetes incidence, and methylation score was higher among Indian Asians [17]. This study provides new insights into the role of epigenetics as a risk factor for T2DM.

Thin-fat Indian concept

India has a lower obesity rate but a prevalence of metabolic abnormalities, such as hyperglycemia, low HDL-cholesterol, and elevated triacylglycerol, that are comparable to or even higher than western countries [14, 18–20]. In other words, Indians have a tendency to become metabolically obese even with normal weight. The anthropometric and biochemical profile of Indian diabetics are different from the western population. Indians have a smaller body size and thinner limbs, which is suggestive of smaller muscle mass. However, in spite of being thin, they are centrally obese (Fig. 1), with a higher waist-to-hip ratio (WHR) and tend to have higher visceral fat and profoundly higher rates of insulin resistance and metabolic syndrome than Europeans [21, 22]. This phenotype has been termed as thin-fat Indian. Mechanisms underlying this central obesity risk among South Asians remain unclear. Even though family studies have shown that central obesity is heritable in South Asians [23, 24], in a recent study among 10,318 South Asians, risk allele frequencies were not higher in South Asians compared to Europeans at known WHR loci, and genome-wide and exome-wide analyses showed no new associations between genetic variants and WHR. This study argues against an important contribution for genetic variants underlying the increased risk of central obesity in South Asians [25].

The bad metabolic profile among Indians is due to a relatively higher proportion of visceral fat. The metabolically inert superficial subcutaneous adipose tissue compartment in the lower extremities is less in Indians compared to Europeans. When energy excess induces obesity, the storage capacity of

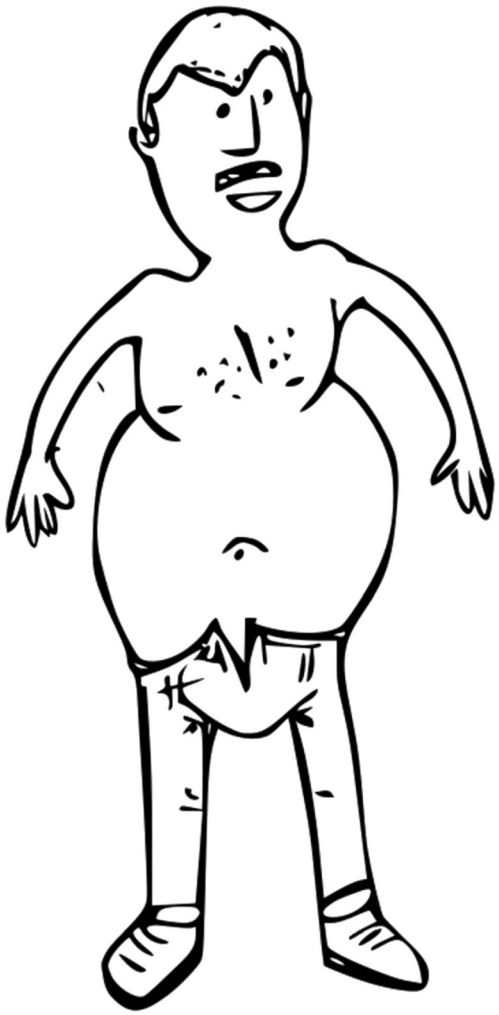

Fig. 1 An illustration of the 'thin-fat Indian' having central obesity with lower skeletal muscle mass and thin and short extremities

the superficial subcutaneous adipose tissue compartment is rapidly exhausted and fat accumulates in the visceral depots, which is metabolically harmful [26, 27]. Considering the above facts, body mass index (BMI) cut-off for overweight and obesity needs to be tailored for the Indian population. (Table 1). The World Health Organization (WHO) in 2004 recommended that for many Asians, for public health action, 23–27.4 kg/m^2 is overweight and 27.5 kg/m^2 or higher is obesity, as against the international cut-off of 25 and 30 kg/m^2, respectively [28]. Guidelines for obesity and overweight based on BMI for Asian Indians were relooked in 2008, and a consensus was developed through discussions by the Prevention and Management of Obesity and Metabolic Syndrome group. This consensus categorised overweight as a BMI of 23.0–24.9 kg/m^2, and obesity as a BMI ≥ 25 kg/m^2 [29].

Waist-hip ratio (WHR) is a simple measure of central obesity. It is the dimensionless ratio of the circumference of the waist to that of the hips [30]. Central obesity usually correlates well with the amount of the visceral fat [31]. Considering the bad metabolic consequences associated with central obesity, WHR would be a better method than BMI to assess cardiovascular and diabetes risk [32]. This is particularly true in Asian Indians due to high prevalence of central obesity with BMI being in normal range. Central obesity is defined as WHR above 0.90 for males and above 0.85 for females [30].

Diabetes in low body weight group (BMI < 18 kg/m2)

A study of 9873 patients with T2DM in India revealed that 3.5% were lean with a BMI < 18.5 kg/m^2 [33]. It was also highlighted that HbA1c, fasting and postprandial blood glucose levels, and microvascular complications were higher among those in the lean group [33]. The major pathophysiology in this group appears to be rapid beta cell failure as opposed to insulin resistance, as highlighted by the fact that they do not have central obesity, have a higher prevalence and early initiation of insulin use, and have biochemical parameters consistent with lower insulin resistance [34–37]. The pathogenesis for this type of T2DM is yet to be elucidated.

Environmental contaminants in the pathogenesis of type 2 diabetes mellitus

Environmental contaminants like pesticides might also play an important role in the pathogenesis of diabetes in India, especially in the rural population involved in agriculture. A meta-analysis of 13 studies revealed pesticide exposure as an increased risk of T2DM; odds ratio of 1.61 (95% CI 1.37–1.88) [38]. A recent study among 3080 people from rural India indicated a high prevalence of diabetes (18.3%) among the

Table 1 Body mass index cut-off for overweight and obesity

	International cut-off (kg/m^2)	South Asians (WHO* 2004) (kg/m^2)	Indian population (PMOMS** group 2008) (kg/m^2)
Over weight	25.0–29.9	23.0–27.4	23.0–24.9
Obesity	≥ 30.0	≥ 27.5	≥ 25.0

*World Health Organization

**Prevention and Management of Obesity and Metabolic Syndrome group

people directly exposed to organophosphate insecticides while it was threefold lesser (6.2%) among the indirectly exposed group. There was a strong association between plasma organophosphate residues and HbA1c levels in this study. Gut microbial degradation of organophosphate insecticides inducing glucose intolerance via gluconeogenesis was the possible mechanism suggested [39]. Many more contaminants in the environment and food can be involved in the pathogenesis of T2DM in India, but is yet to be investigated.

Urban-rural differences in India

National data show the prevalence of diabetes to be double in urban areas than that of rural areas. In the multicentric study conducted by Indian Council Of Medical Research during 2003–06, the prevalence of diabetes among men and women was 11.4 and 10.3% in urban areas and 6.2 and 5.7% in rural areas, respectively [40]. Interestingly, in the same study, the data from the state of Kerala showed a paradoxically higher prevalence of diabetes in rural than urban dwellers; 19% in rural men and 22% in rural women compared to 12% in urban men and 17% in urban women [41]. This contrasting data from Kerala may be due to the rising rural household food consumption mainly because of the effective public distribution system (PDS) [42]. Food items supplied through PDS at subsidised rates are predominantly cereals [43]. Pulses, vegetables, and fruits do not come under PDS. Also, over the past few decades, there is a huge shift from manual labour to physically less demanding office jobs among rural Keralites. As a consequence, their diet has carbohydrates in excess of their energy demands, but is deficient in pulses, animal proteins, fruits, and vegetables.

Microvascular complications among Indian diabetics

Increased incidence of diabetes at a younger age and increased longevity due to modern health care facilities will give an opportunity for a large number of diabetic individuals to develop various microvascular and macrovascular complications. It was observed that Indians with T2DM develop microvascular complications much faster, when compared to the western population [44]. Reasons that can be postulated for this rapid progression are:

- Late diagnosis of cases, as screening programmes to detect diabetes mellitus are in a nascent stage in India [45].
- Poor glycemic control in the initial years of diabetes due to irregular treatment and switching to alternative systems of medicine [46].

The UK Prospective Diabetes Study (UKPDS) and Diabetes Control and Complications Trial (DCCT) have demonstrated that patients with intensive glycemic control in the initial years developed less microvascular complications on long-term follow-up [47, 48]. The lack of strict initial glycemic control may be one of the important factors responsible for faster progression to microvascular complications.

- Lack of incorporation of HbA1c testing in the routine diabetic care.

HbA1c is the gold standard test around the world for monitoring glycemic control, but the usual practice in India is to target fasting blood sugar (FBS) and postprandial blood sugar (PPBS). HbA1c can be grossly deranged even if FBS and PPBS are in control, as lunch or dinner is usually the largest meal among most Indians. Blood sugar surge following lunch and dinner are thus never addressed. In the Delhi Diabetes Community (DEDICOM) survey conducted among urban diabetics from middle- and high-income groups, only 13% of respondents had undergone HbA1c testing and only 21.7% had heard of HbA1c testing [49].

- Late initiation of Insulin therapy due to financial constraints, needle phobia, and fear of bad reputation among physicians [50].

Prevention strategies

Dietary modifications and increase in the physical activity are the two crucial components in preventing T2DM. Dietary modifications cannot simply be delivered by giving a patient a diet sheet in a one-size-fits-all approach. Dietary modifications that are too complex to follow or deviate grossly from the routine pattern followed for long years are difficult to adhere to; poor compliance will be the end result. It is more practical if one is allowed to continue the same dietary pattern if it is not grossly unbalanced, but simultaneously reducing excess carbohydrate intake in each meal and increasing intake of pulses, vegetables, and fruits. Many vegetable side dishes and curries used in India often feature potato and other tubers, which are carbohydrate-heavy, and hence should be addressed in the advised dietary modifications. Dividing the meals into frequent small meals is also helpful by preventing severe escalations of postprandial blood sugar. There is a popular belief that diet based on wheat is better than rice for diabetes. Even though food items made from wheat will produce early satiety [51], and have a glycemic index slightly less than rice [52], what ultimately matters is the amount of carbohydrate ingested. Meat and fish are good sources of protein, and there is no theoretical harm in regular intake, but a practical risk is

that one will tend to consume carbohydrate (cereals) when taste-enhancing non-vegetarian side dishes are used. All adults, particularly those with type 2 diabetes, should decrease the amount of time spent in daily sedentary behaviour. Prolonged sitting should be interrupted with bouts of light physical activity such as walking, leg extensions, or overhead arm stretches every 30 min [53]. Physical activity recommended is at least 150 min/week (30 min/day for 5 days a week). This is particularly important in populations at high risk and with prediabetes [53].

Diabetes awareness in India

Knowledge and awareness regarding diabetes are grossly inadequate in India. In the Chennai Urban Rural Epidemiology Study (CURES-9), only 22.2% of the whole population and 41.0% of the known diabetic subjects were aware that diabetes could be prevented. Knowledge of the role of obesity and physical inactivity in causing diabetes was very low, with only 11.9% of study subjects reporting these as risk factors for diabetes. Only 19.0% of the study population knew that diabetes could cause complications [54]. In the Indian Council of Medical Research India Diabetes Study (Phase I) conducted in representative samples of four geographical regions of India—Chandigarh, Tamil Nadu, Jharkhand, and Maharashtra, only 43.2% of the overall study population had heard about a condition called diabetes. Among the general and diabetic population who knew about diabetes, only 56.3 and 63.4%, respectively, were aware that diabetes could be prevented [55]. These studies underscore the need for conducting large-scale diabetes awareness and education programmes.

Does genomic profiling to assess type 2 diabetes risk improve health outcomes?

There is clear evidence available from diabetes prevention studies that prevention works equally better in individuals with heightened genetic risk and in individuals with no such risk, an argument to emphasise lifestyle modification as the means for all to prevent the development of diabetes, irrespective of the genetic risk status [56, 57]. Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group discourages clinical use of genetic testing until further evidence supports improved clinical outcomes [58].

Conclusions

Lifestyle factors play a far greater role in the ongoing epidemic of diabetes when compared to genetic risk. This epidemic is occurring in a genetic background that has been relatively static for centuries, whereas lifestyle is undergoing rapid change. However, a potential gene environment interaction cannot be ruled out. Risk alleles identified to date through genome-wide association studies have been able to explain only less than 10% of the observed heritability. Acquisition of the same unhealthy lifestyle from parents could be the major reason for the observed heritability that genetics could not explain. High-calorie, low-activity lifestyle by India's growing middle class are the major causes for the current diabetic epidemic in India. More emphasis should be given for epidemiological studies and formulation and implementation of community level preventive strategies.

Author contribution All authors contributed equally to the work, participating in collection of the data and writing the manuscript and approving the final version of it.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors. Informed consent was obtained from all individual participants included in the survey.

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