Are Indians Destined to be Diabetic?

Sumedh S Hoskote*, Shashank R Joshi**

Indians lead the world with the greatest number of diabetics (42 million) and it is estimated that this number will swell to 69.9 million by the year 2025. With its chronic course, we can expect diabetes to have a serious adverse impact on the life expectancy as well as the quality of life in India. The increasing modernization and adoption of a more sedentary lifestyle in rural and urban India has taken its toll on the health of the populace, only compounding the risk for diabetes and cardiovascular disease. Awakening to similar concerns, the Government of India recently launched the Pilot Phase of the National Programme for Prevention and Control of Diabetes, Cardio-vascular Diseases and Stroke (NPCDS) in seven states. Apart from health promotion and educative measures, the programme aims to collect data on various crucial determinants of diabetes pathogenesis such as diet, physical exercise, body mass index (BMI), blood glucose and lipids.

It has been observed, since long, that Indians are more insulin resistant compared to other ethnic groups and develop type-2 diabetes at a younger age. Apparently healthy Asian Indians have been found to exhibit features of insulin resistance. It has been shown that Indians demonstrate a higher glycemic response to all foods and that Indians secrete more insulin in response to glucose, when compared with Europeans.

For centuries, Indians were largely a vegetarian-diet consuming, agrarian population. This provided a lower energy density, in comparison to the predominance of meat in the diet of Europeans. When the emigration to Europe took place 40000 years ago, the continent had sparse vegetation due to the harsh winters, and humans consumed energy-rich meat products to survive. It has been proposed that obesity and type-2 diabetes had their roots in a natural selection of these early humans, favouring a “thrifty genotype”, which enabled highly efficient storage of energy during periods of food abundance. Similarly, the “thrifty phenotype” explains how low-birth-weight babies, who have been exposed to a chronic energy-deprived state, hoard energy stores and go on to develop type-2 diabetes in adulthood. A corollary of these hypotheses is that these genetic or phenotypic adaptations that are useful in an energy-deprived state become disadvantageous when the dietary energy intake becomes high and physical activity level drops. Given the central role of the mitochondria in the energy balance of the cell, mitochondrial function in the setting of diabetes or insulin resistance has received much attention in recent literature.

Insulin has been shown to enhance muscle mitochondrial biogenesis in humans and in people with type 2 diabetes increasing insulin from the post-absorptive to post-prandial level does not increase ATP production unlike in non-diabetic people. Another study showed that uncoupling of beta-oxidation of fatty acids and the TCA cycle, which is induced by chronic inactivity and a high-fat diet, causes both insulin resistance as well as intramyocyte accumulation of partially oxidized lipids. Moreover, mitochondrial dysfunction has been reported to be crucial to the pathogenesis of non-alcoholic fatty liver disease – one of the associated disorders of insulin resistance, especially among Asian Indians. A study on Asian Indians showed that levels of intramyocyte lipid correlated with type-2 diabetes, waist circumference and waist-hip ratio, but no association was found with insulin resistance. Mitochondrial dysfunction in insulin resistant states especially in type-2 diabetes is a candidate for intensive research in the field of diabetology.

A recent landmark study in Diabetes by Nair et al. compared Asian Indian diabetics, Asian Indian non-diabetics and North-European (NE) American non-diabetics for mitochondrial function, in addition to insulin sensitivity, intramuscular triglyceride, lipid profile and proinflammatory markers like Interleukin-6 (IL-6), C-Reactive Protein and Tumor Necrosis Factor-alpha. Indians, diabetic or otherwise, had significantly more insulin resistance when compared to non-diabetic NE Americans. Despite this, Indians had no evidence of subnormal mitochondrial functioning, in fact demonstrating a higher mitochondrial DNA copy number, higher Maximum ATP Production Rate (MAPR) as well as upregulation of the expression genes coding for the oxidative phosphorylation and Krebs’ cycle enzymes. This led the authors to conclude that, in Asian Indians, insulin resistance and mitochondrial dysfunction may be unrelated. It remains to be determined whether the higher capacity to produce ATP may contribute to their energy balance when they ingest high caloric density diet. Another interesting result was that intramuscular triglycerides (IMTG) were

**Department of Endocrinology, Seth G. S. Medical College and KEM Hospital, Mumbai, India; Endocrinologist, Lilavati Hospital and Bhatia Hospital, Mumbai. *Research Associate, Joshi’s Clinic, Mumbai.

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higher in the non-diabetic Indians compared to the non-diabetic NE Americans, whereas there was no difference between the diabetic Indians and the non-diabetic Americans. This finding implies that insulin resistance and type-2 diabetes may not have the same association with IMTG, or that IMTG is associated closer with an incidental entity, such as obesity. Proinflammatory markers were also found to be significantly higher in the diabetic Indians, corroborating the association.

Since this study consisted of non-resident Indians, more data from resident Indians would be needed to examine the relative effects of genetic and environmental factors on mitochondrial function in Indians with or without diabetes. Also, a comparison with NE American diabetics could have offered a deeper insight into potential interaction between mitochondrial function and diabetes. It is, however, known that NE American diabetic people have similar mitochondrial DNA copy number and ATP production in the post-absorptive insulin levels as in non-diabetic controls, although insulin induced increment of ATP production is defective in the diabetic people. In contrast, as people become older, they develop insulin resistance and an associated decline in mitochondrial function, but, unlike in type-2 diabetes, the age-related mitochondrial dysfunction and insulin resistance occur along with a progressive decline in mitochondrial DNA copy number. The paradox in Indians is that they have higher mitochondrial DNA abundance in association with insulin resistance.

The reported study is the first step towards understanding the potential role of environmental adaptation of energy metabolism and in developing insulin resistance and type-2 diabetes in Asian Indians. The seminal novel information from the current study could form the basis of future studies to fully understand the exact role of mitochondria which are the main sites of all fuel and energy metabolism, in the pathogenesis of type-2 diabetes. These may also shed light on the mechanisms of how adaptation from low energy to high energy environment may lead to a predisposition to developing diabetes. Also, further investigation is needed to explore the relationship between proinflammatory markers and type-2 diabetes in Indians. Novel targets for investigation in the Indian population include IL-6 promoter polymorphisms (associated with diabetes in Native Americans and Caucasians) and insulin-mediated regulation of gene expression of metabolic enzymes such as hexokinase II. Given that genetic factors could be responsible in the pathogenesis of type-2 diabetes, the likelihood of variation amongst Indian communities cannot be ruled out and should be taken into account while designing and interpreting studies.

It is imperative at this stage that diabetes pathogenesis is understood from the Indian perspective. The current data clearly indicate that Indians are, perhaps, metabolically different from Europeans and the diet and medications may be handled differently in these two populations. A better understanding about the cause of a predisposition of Indians to become diabetic will go a long way in planning healthcare policy and delivery in the coming years, in order to ensure that the burden of disease is reduced.

REFERENCES