

Ethnicity, type 2 diabetes & migrant Asian Indians

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The rapid increase of diabetes prevalence in the US population and across all westernized world has been associated with environmental changes that promote obesity. However, studies conducted in various ethnic groups within the US population have pointed out differences in susceptibility to diabetes within the same environmental pressure. Of particular interest is the growing evidence that Asian Indians, *i.e.*, persons originating from the Indian Subcontinent, are at uniquely heightened risk for type 2 diabetes when compared to other populations. The elucidation of the mechanisms responsible for the heterogeneous relationship between obesity and type 2 diabetes in various ethnic groups, and particularly in Asian Indians, may give important contributions to better understand the complex mechanisms involved in the development of type 2 diabetes. This review examines epidemiological and pathophysiological aspects of the interaction between environment and ethnic predisposition to type 2 diabetes in Asian Indians migrated to the US.

Key words Asian Indian - beta-cell dysfunction - ethnicity - insulin resistance - type 2 diabetes

Asian Indians have been reported to be at high risk for type 2 diabetes¹⁻⁴, a major cause of disability and mortality in Western countries. The incidence of diabetes is also increasing in developing countries, including those in the Indian Subcontinent. Obesity and central fat distribution are important predictors of both diabetes and cardiovascular disease, and appear to play a major pathogenetic role in these two disease entities. The growing westernization of Asian Indian countries and adoption of “obesogenic” life-style may therefore contribute to the alarming increase in prevalence of diabetes. However, recent studies suggest that Asian

Indians are at increased risk for any level of obesity and central fat distribution, when compared to European descent persons^{1,4}. It is possible that ethnic-related life-style factors, including diet, may explain some of the excessive risk. However, a major role may be played by genetic susceptibility. This review summarizes the data available on the complex interaction between environmental and genetic factors in the pathogenesis of diabetes with particular emphasis on the migrant Asian Indian population. The implications for diabetes and cardiovascular disease management and prevention are also discussed.

Epidemiological evidence for ethnic predisposition to type 2 diabetes in Asian Indians

A wealth of epidemiological data shows that the prevalence of diabetes in various ethnic groups is influenced by environmental factors⁵⁻¹⁰. This is also true for Asian Indians. It has been reported that Asian Indians living in rural areas of India have a prevalence of diabetes of about 2 per cent. Asian Indians living in urban India have a prevalence of diabetes of about 8 per cent. Asian Indians migrated to UK or other “westernized” countries, such as Singapore and Fiji, have about four times higher prevalence of diabetes compared to those living in India^{1,3,4}. This observation suggests that the life-style changes associated with the process of urbanization/westernization may largely explain the progressive increase in the prevalence of type 2 diabetes. However, comparison with the prevalence of diabetes in Asian Indians and European descent persons living within the same environmental conditions, suggest that Asian Indians have unusual excess of type 2 diabetes, incompletely explained by life-style factors and related traditional risk factors⁴. We will now review the data on the impact that acquired factors related to urbanization and adoption of western life style may have on the risk for type 2 diabetes in Asian Indians.

Relationship between life style factors and risk for type 2 diabetes in Asian Indians

Diet and exercise: Reduced fiber intake and increased consumption of animal fats and processed carbohydrates are the main changes in dietary habits described in westernized societies and adopted by migrant populations. Both animal fats and carbohydrates have been associated with excessive predisposition to diabetes, mainly through development of obesity^{11,12}. Reduced fiber content in the diet has also been associated with increased predisposition to diabetes^{13,14}. Besides diet composition, higher daily energy intake, related to consumption of saturated fats and refined carbohydrates, predisposes to obesity and type 2

diabetes. For each kg of weight gain it has been calculated that the risk for diabetes increases by about 4.5 per cent¹⁵.

There are no detailed data available on the changes in dietary habits in Asian Indians who migrate to western countries. However, studies conducted in other ethnic groups living in US have shown that changes in dietary habits of migrant populations are related to the process of acculturation. One study that compared the dietary content of similarly aged Japanese-American men living in Seattle with that of Japanese men in Japan showed that the Japanese-American diet was higher in calories, protein, fat and carbohydrates¹⁶. The mean daily intake of fat in Japanese-American men was 32.4 g, in contrast to a mean intake of only 16.7 g of fat in Japanese men. These studies have shown that, for many Asian Americans, their diet in America is higher in calories and fat and lower in fiber than in their countries of origin. The acculturation experience of Japanese immigrants and their descendants in the US is historically and culturally unique. The traditional diet of the Japanese was fish- and vegetable-based until the end of the nineteenth century. A study conducted in Los Angeles indicated that food patterns and food choices have changed in succeeding generations of Japanese-Americans from traditional diet to a diet containing many complements and accessory foods that are higher in fat, sugar, sodium and calories¹⁷. The studies in migrant Japanese confirm that succeeding generations of immigrants maintain intake of food attached to their cultural identity longer than food that enhance the taste and palatability of basic foods. When new food is incorporated into diet of immigrants, they frequently include accessory food group, including sweets, snacks and soft drinks. Excess intake of accessory food may contribute to increased intake of fat, sodium, sugar and calories.

Another study conducted in Asian populations includes a comparison of dietary habits and physical activity between Chinese in North America and those living in China. Differences included higher meat and

dairy products intake in the Chinese living in North America with about 35 per cent of the daily caloric intake from fat (as compared to 22% in the Chinese living in China) and 48 per cent of calories from carbohydrates (as compared to 62-68% in the Chinese living in China)¹⁸.

Reduced physical activity is observed in association with the “urbanization and westernization” process and seems to affect risk of diabetes independently of diet. The level of physical activity has been reported to be higher in ethnic groups living in their countries of origin as compared to the same ethnic groups living in US¹⁸.

The effects of changes in dietary habits and exercise levels, on the excessive prevalence of type 2 diabetes in Asian Indians who have migrated to the US remains to be elucidated.

Pathophysiology of type 2 diabetes in migrant Asian Indians: beta-cell dysfunction vs. insulin resistance

The pathogenesis of type 2 diabetes involves both insufficient insulin secretion and insulin resistance. As described by Bergman *et al*¹⁹ the relationship between insulin secretion and insulin resistance can be mathematically described as a hyperbole where the product of insulin resistance and insulin secretion is constant. Kahn *et al*²⁰ demonstrated that such a relationship is present across a wide range of insulin sensitivity in people with normal glucose tolerance. A study in the Danish population showed the large variability in the relationship between insulin sensitivity and insulin secretion in young European men and women²¹. A given individual may be severely insulin resistant but maintain normal glucose tolerance if beta cell secretory capacity matches the degree of insulin resistance. On the other hand, an individual may have a low beta cell secretory functional capacity but maintaining normoglycaemia if insulin sensitivity is maintained to match for the low beta cell function. The predominant mechanism leading to a shift of the constant relationship between

insulin resistance and beta cell function, leading to impaired glucose tolerance (IGT) and diabetes could theoretically differ in various individuals or groups. The UK Prospective Diabetes Study (UKPDS) group included type-2 diabetic patients from three major ethnic groups²², where most of the patients (82%) were whites, 10 per cent were of Asian Indian origin and 8 per cent were of Afro-Caribbean origin. Insulin resistance was highest in the Asian Indians, followed by the white Caucasians and by the Afro-Caribbeans. On the contrary, beta cell function was best in Asian Indian diabetics and worse in the Afro-Caribbeans. The beta cell function of white Caucasians was between the two other ethnic groups. So, although both insulin resistance and reduced insulin secretion are involved in the pathogenesis of type 2 diabetes, the predominant mechanism appears to be different in various ethnic group: Asian Indians seem to have insulin resistance as the predominant mechanism leading to diabetes.

The question at this point is: what is the basis of excessive insulin resistance in Asian Indians? To answer this question we will describe the known factors that contribute to the pathogenesis of this complex condition and how these pathogenetic factors may contribute to explain excessive insulin resistance in migrant Asian Indians.

Excessive insulin resistance in migrant Asian Indians

Migrant Indians were shown to have increased insulin resistance and hyperinsulinaemia compared to Europeans^{23,24}. Studies performed in various ethnic groups and in both genders have shown that increasing body fat content is linearly and inversely related to insulin resistance²⁵⁻²⁹. The mechanisms whereby insulin-mediated glucose disposal is impaired in human subjects with obesity are incompletely understood. Defective insulin signaling in both the skeletal muscle and the adipocyte seems to play a role. Obese human subjects have decreased tyrosine kinase activity in skeletal muscle cells³⁰ and adipocytes³¹. Receptor tyrosine kinase activity is

restored by weight loss, which also improves insulin sensitivity. Obesity is also accompanied by reduced phosphorylation of downstream proteins that mediate intracellular insulin signaling: insulin receptor substrate-1 (IRS-1) and regulatory subunit of the phosphatidylinositol-3 (PI-3) kinase³². As a consequence obesity associates with reduced mobilization of glucose transporter (GLUT-4) containing vesicles from the intracellular domain and reduces the GLUT-4 mediated influx of glucose into the skeletal muscle cells, the main site of insulin-mediated glucose disposal. Obesity may induce decreased insulin signaling in the skeletal muscle by promoting triglycerides accumulation in the muscle cells.

Excessive mobilization of free fatty acids from insulin resistant adipocytes in obesity may contribute to excessive accumulation of triglycerides in the skeletal muscle cells. Adipose tissue may affect insulin signaling in the skeletal muscle through alternative pathways. Adipose tissue has been shown to produce tumour necrosis factor alpha (TNF- α), leptin, resistin and adiponectin, which may have an impact on insulin signaling in the skeletal muscle cells, independently of the effects of fatty acids and triglycerides accumulation. TNF- α is a protein that is over-expressed in adipocytes of obese patients³³ and appears to have a paracrine function. In the same adipocytes or surrounding skeletal muscle cells, TNF- α may increase serine phosphorylation of the insulin receptor and also of IRS-1³⁴ and possibly other proteins that mediate intracellular insulin signaling. Serine-phosphorylated IRS-1 has been shown to inhibit insulin receptor tyrosine kinase activity, which leads to impaired downstream insulin-signaling³⁵. Leptin is an adipocyte-derived hormone which increases in response to fat accumulation and reduces appetite through hypothalamic effect³⁶. Leptin also contributes to reduce intracellular content of triglycerides. Leptin resistance appears to reduce these physiological functions of leptin and contribute to maintain excessive FFA flux and intracellular accumulation, leading to insulin resistance and also contributing to beta-cell dysfunction³⁷. Resistin³⁸ and

adiponectin³⁹ have also been identified as adipocyte products which could play a role in mediating reduction of skeletal muscle sensitivity to insulin in obese subjects. So, clearly the development of obesity has an impact on the development of both insulin resistance and beta cell dysfunction. On the other hand, in non obese subjects a significant variability of insulin sensitivity has been uniformly observed. In fact, only 50 per cent of the variability of insulin sensitivity is explained by obesity. Therefore, some individuals may be severely insulin resistant despite minimal accumulation of body fat. This is particularly important for Asian Indians who seem to develop insulin resistance even in absence of obesity, at lower BMI than Caucasians. Since despite the absence of obesity, the Asian Indian population seems to be characterized by a tendency towards truncal accumulation of fat, some investigators have proposed that the excessive insulin resistance in Asian Indians could be explained by an abdominal fat distribution which, in turn, may be genetically determined. Banerji *et al*⁴⁰ proposed that excessive visceral adiposity in the Asian Indians could account for excessive insulin resistance in this ethnic group. Similar data were reported by Raji *et al*⁴¹. However, these two studies lacked a direct comparison of the relationship between obesity and insulin resistance in the two ethnic groups taking into account both generalized adiposity and fat distribution. To define the role of adiposity and fat distribution in the excessive insulin resistance of Asian Indians we performed hydrodensitometry, skinfolds measurements and euglycaemic-hyperinsulinaemic clamps in 21 healthy Asian Indian men and 23 caucasian men of similar age and body fat content⁴². Despite similar total body fat content, Asian Indians had higher truncal adiposity than caucasians. In both Asian Indians and caucasians, the insulin sensitivity index was inversely related with both total body fat and sum of truncal skinfolds thickness, a measure of truncal adiposity that independently predicts insulin resistance. After adjustment for total body fat and truncal skinfolds thickness, Asian Indians still had excessive insulin resistance compared to the caucasians. For any level

of truncal skinfolds thickness Asian Indians were significantly more insulin resistant than the caucasians. These results are consistent with the hypothesis that neither obesity nor fat distribution explains the excessive insulin resistance and type 2 diabetes in this ethnic group.

Because of the mechanistic link between adipose tissue metabolites, such as non esterified fatty acids (NEFA), adiponectin and leptin, and insulin resistance, we recently evaluated whether Asian Indians who are not obese, exhibit changes in adipokines that associated with their obesity-independent excess of insulin resistance⁴³. We observed that plasma concentrations of adipose tissue metabolites leptin and adiponectin were higher and that of adiponectin was lower in insulin-resistant Asian Indians compared with more insulin sensitive caucasians. Taken together, these data point to a primary defect in adipose tissue of Asian Indians that determines metabolic changes commonly associated with obesity even in absence of body fat/fat distribution abnormalities. The possibility exists that the observed abnormalities have a genetic basis. Evaluation of genetic factors that may interact with obesity and fat distribution in determining excessive insulin resistance in Asian Indians is currently undergoing in our lab. On this line we recently reported on the possible role of ectonucleotide pyrophosphatase phosphodiesterase 1 (ENPP1). ENPP1 belongs to a family of enzymes (ENPPs) which are known to hydrolyze 5'-phosphodiesterase bonds in nucleotides⁴⁴. Five members of this family (ENPP1-5) have been identified, and current evidence suggests that ENPPs have multiple and related physiological roles, including nucleotide recycling, modulation of purinergic receptor signaling, regulation of extracellular pyrophosphate levels, stimulation of cell motility, and a possible role in regulation of insulin receptor signaling. The latter function has been more specifically related to ENPP1, a widely expressed class II transmembrane glycoprotein, which could interact with the insulin receptor and decrease insulin-induced tyrosine phosphorylation of its intracytoplasmic domain. There are evidences showing that a physical interaction occurs on the cell surface between ENPP1

and the insulin receptor, preventing insulin-induced conformational changes of the extracellular receptor alpha subunit⁴⁵. This failure impairs beta subunit autophosphorylation and tyrosine-kinase activity, thus switching off insulin signaling^{44,45}. A common ENPP1 variant, the K121Q has been shown to determine a gain of function for the protein⁴⁶. We have recently reported that ENPP1 121Q is associated with excessive insulin resistance in Asian Indians living in Dallas and explains almost entirely the ethnic differences in insulin resistance between the Caucasians and the migrant Asian Indians of our cohort⁴³. More recently we have shown that ENPP1 121Q variant is also associated with increased risk for type 2 diabetes in Asian Indians living in Dallas and also in Asian Indians living in Chennai⁴⁷.

Conclusions

Excessive insulin resistance in migrant Asian Indians appears to be the likely mechanism for the excessive prevalence of diabetes in this population. Although there is no doubt that westernization and acculturation process will contribute to the growing prevalence of type 2 diabetes in the Asian Indian population, current evidence points to possible genetic factors that modulate susceptibility to insulin resistance and type 2 diabetes. We have recently described a genetic variant that appears to contribute to excessive susceptibility to insulin resistance and type 2 diabetes in Asian Indians: the ENPP1 121Q. Future studies aimed at evaluating the interaction between ENPP1, as well as other genes involved in the pathogenesis of insulin resistance, and diet/exercise can help identifying the mechanisms of insulin resistance in migrant Asian Indians and will possibly help identifying targets of treatment to prevent the potential epidemic of type 2 diabetes in this population.

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