Review

INSULIN RESISTANCE IN ASIAN-INDIANS

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Asian-Indians have been described to have excessive insulin resistance compared to other ethnic groups. This is particularly true in Asian-Indians who migrate to "westernized" countries. The reasons underlying the observed inter-ethnic differences are not completely understood. In general, inter-ethnic differences in insulin resistance may have an environmental or genetic explanation. The main acquired factors that seemingly increase insulin resistance in all ethnic groups include obesity, sedentary life style, nutrition rich in animal products and aging. Among these different environmental determinants of insulin resistance, nutrition, lack of exercise and obesity may be part of the so called "westernization" process in migrant Asian-Indians which can induce excessive insulin resistance and therefore explain the increased prevalence of type 2 diabetes in urbanized and migrant Asian-Indians.

DIET AND INTER-ETHNIC DIFFERENCES IN INSULIN RESISTANCE: High fat diets have been implicated in the etiology of insulin resistance and glucose intolerance. Clinical studies have revealed adverse effects of experimental high fat, low-carbohydrate diets on glucose and insulin metabolism in some [1,2] but not in all [3] instances. Insulin resistance can be induced in laboratory animals by diets high in fat, fructose or sucrose. Habitual intake of dietary fat has been positively related to insulin resistance in several studies of non-diabetic individuals. Using estimates of insulin sensitivity based on homeostatic modeling, Fesken et al. [4] reported significant adverse associations of total dietary fat, saturated fat, and monounsaturated fat intakes with insulin sensitivity, independent of body mass index, although no significant association was observed for polyunsaturated fats. Lovejoy and DiGirolamo [5] showed habitual, high fat diets to be related to worsened insulin sensitivity as measured by an intravenous glucose tolerance test in 45 lean and obese subjects, but this association was no longer significant after adjustment for obesity. The insulin resistance atherosclerosis study (IRAS) measured insulin sensitivity directly by frequently sampled intravenous glucose tolerance test and included 1625 men and women of non-Hispanic white, African-American, and Hispanic ethnicity [6]. Total fat intake was inversely related to insulin sensitivity, but this association was not significant after adjustment for body mass index (BMI) and waist hip ratio (WHR). These findings were consistent in all ethnic groups studied. Some other studies have suggested that high carbohydrate intake reduces insulin sensitivity in humans. Schonfeld et al. [7] compared a group of vegetarians of Asian Indian descent to a group of vegetarians of European descent. The Asian-Indians had excessive insulin resistance despite similar dietary intake. In another study, diet composition did not contribute to the excessive insulin resistance of Asian-Indians living in London [8]. Therefore, the available data exclude dietary changes playing a role in the inter-ethnic differences in insulin resistance.

EXERCISE AND INTER-ETHNIC DIFFERENCES IN INSULIN RESISTANCE: In a study of Rosenthal et al. [9], sedentary life-style was associated with insulin resistance independent of generalized obesity and age in non-diabetic individuals. Therefore, it is possible that lean individuals who do not exercise are insulin resistant, despite the absence of obesity. Lack of exertion is also common in urban dwellers of India and in migrants to UK or US. However, in a study by McKeigue et al. [10] it was shown that leisure time activity, but not working activity was decreased in migrant Asian-Indians living in UK. Lack of leisure time activity did not explain the inter-ethnic differences in insulin resistance between Asian-Indians and Europeans.

OBESITY/FAT DISTRIBUTION AND INTER-ETHNIC DIFFERENCES IN INSULIN RESISTANCE: Studies performed in various ethnic groups and in both genders have shown that increasing body fat content is linearly and inversely related to insulin resistance [11-15]. On the other hand, in lean subjects a significant variability

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of insulin sensitivity has been uniformly observed. Therefore, some individuals may be significantly insulin resistant despite minimal accumulation of body fat. One factor that contributes to the complexity of the relationship between obesity and insulin resistance is the way fat is distributed. Several studies have demonstrated that when fat is distributed preferentially in the abdominal area, insulin-mediated glucose disposal is reduced, independent of overall degree of adiposity [13-15]. Therefore, it is conceivable that even in the absence of significant accumulation of total body fat, even a minimal deposition of fat in the abdominal area may induce insulin resistance. A typical example of the effects of fat distribution on insulin resistance and excessive prevalence of type 2 diabetes is provided in the studies of W. Fujimoto et al. [16,17] in migrant Japanese. Japanese who live in Japan have low prevalence of obesity and type 2 diabetes compared to White-Americans [18]. However, Japanese-American migrated to Hawaii have higher prevalence of abdominal obesity and type 2 diabetes that becomes even more prevalent in Japanese-Americans living in Continental US [18,19]. Ethnic groups, such as the Hispanics and the Asians that are more prone to develop abdominal obesity have more insulin resistance than the African-Americans or White-Americans, who develop less abdominal obesity for similar degree of generalized adiposity. Ethnic differences in fat distribution could explain the observed excessive prevalence of insulin resistance and diabetes in the Asian Indian population. 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. [20] recently proposed that excessive visceral adiposity in Asian-Indians could account for excessive insulin resistance in this ethnic group. Visceral adiposity, measured by single slice abdominal CT scans, was significantly correlated with insulin resistance in a group of Asian-Indian women living in New York. To define the role of adiposity and fat distribution in the excessive insulin resistance of Asian-Indians we recently performed hydro-densitometry, skinfolds measurements and euglycemic-hyperinsulinemic clamps in 21 healthy Asian-Indian men and 23 Caucasian men of similar age and body fat content [21]. The glucose disposal rate during hyperinsulinemia was significantly lower in the Asian-Indians than in the Caucasians (3.7±1.3 vs 5.3±2.0 mg/min/kg lean body mass; p=0.003). 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. The excessive insulin resistance in Asian-Indians is probably a primary metabolic defect and may account for the excessive morbidity and mortality from diabetes in this ethnic group. Evaluation of factors that may interact with obesity and fat distribution to determine excessive insulin resistance in Asian-Indians is currently undergoing in our laboratory. It is conceivable that Asian-Indians have a specific genetic predisposition to develop insulin resistance. Asian-Indians tend to develop severe insulin resistance even in the presence of only mild increase of body fat. Insulin resistance plays a major role in the excessive prevalence of diabetes in this ethnic group. The understanding of the genetic mechanism and their interaction with acquired factors, particularly fat accumulation, may explain the excessive prevalence of type 2 diabetes in this ethnic group.

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