The Impact of Ethnicity on Type 2 Diabetes

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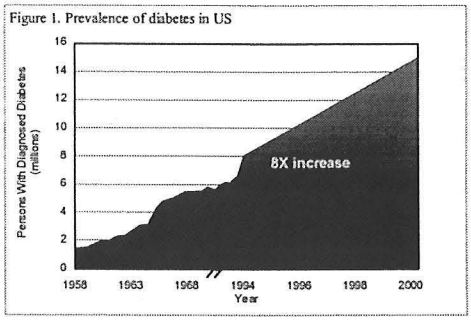
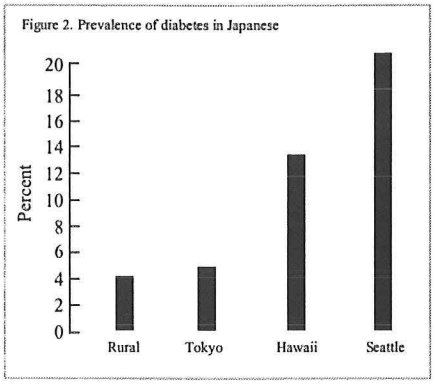
Interests:
1. Etiopathogenesis of insulin resistance and pathophysiology of insulin resistance
2. Management of dyslipidemia, diabetes, obesity and the Metabolic Syndrome
3. Prevention of Diabetes and Cardiovascular Disease

Epidemiology.

Over 15 million US adults (6.3 million men and 8.7 million women) are currently estimated to have diagnosis of diabetes (1). A wealth of epidemiological data show that the prevalence of this disease, mainly type 2 diabetes, has increased significantly over the past several years and continues to increase at an alarming rate not only in the US population but across the entire world (2, 3). The world epidemic of diabetes seems to affect both developed and developing countries and includes populations, such as the Micronesians Nauru, who, previously free of diabetes, were recently shown to have prevalence of diabetes comparable to that of American Pima Indians (prevalence of about 40-50%) (4). Environmental changes related to the "urbanization/westernization" process across all populations of the world have been proposed to play a major role in the diabetes epidemic. This is supported by studies that compare the prevalence of diabetes in ethnic groups living in different environments and by studies comparing prevalence of diabetes in multiethnic environments.



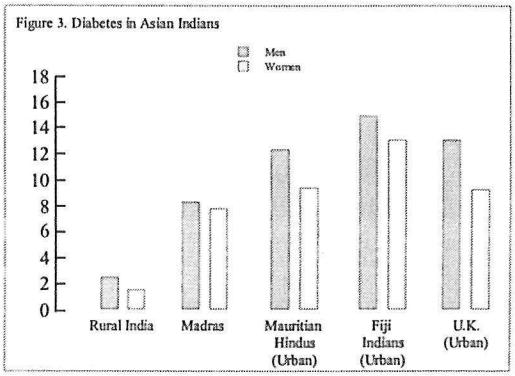
In a survey conducted in 1972 and 1973 in a small rural area of Japan, the prevalence of diabetes was about 4% in the age group 40-69 years (5). A slightly higher prevalence was found in Tokyo for the same age group (6). The prevalence of diabetes has continued to rise in Japanese living in Japan (7) but within the same ethnic group it has been shown to be higher in those living in Hawaii and in continental US than in those living in Japan, reaching over 21% in Japanese living in Seattle, WA (8,9) (Figure 2).



In 1979 through 1981, almost 40,000 people were screened in Beijing with 100 g OGTT and WHO diagnostic criteria for diabetes revealed a prevalence ranging from 2.3% to 9.7% in the various age groups (10), higher than the prevalence recorded in rural China (11). Higher prevalence of diabetes has been observed for Chinese living in Hong Kong, Singapore, Taiwan and Mauritius (12-15).

In Korea, the prevalence of diabetes in rural and small town areas was between 2 and 4.4% in various age groups, whereas the prevalence in Seoul was between 13% and 15.9% in the same age range (16).

Asian-Indians living in rural areas of India have a prevalence of diabetes of about 2%. Asian Indians living in urban India like areas of Madras have a prevalence of diabetes of about 8%. Asian Indians migrated to UK or other westernized Countries, such as Singapore, have about four times higher prevalence of diabetes compared to those living in India (Figure 3) (15,17,18).



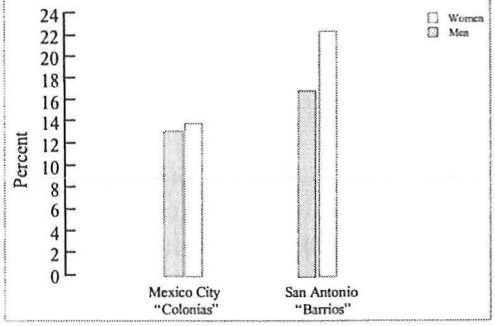
In the Philippines, the diabetes prevalence has been reported to be about 8-10% among adults. In 1982-1983, a national diabetes survey of 12,297 Filipinos aged 20-65 years was conducted in 44 randomly selected urban and rural communities in the Philippines (19). The survey revealed a crude prevalence of diabetes of 2.5% in rural communities, 6.8% in urban areas, and 8.4% in the capital city of Manila. A recent

study conducted among Filipino-Americans living in Houston, Texas, the prevalence of type 2 diabetes was found to be about 16.2% (20).

African-Americans have a prevalence of diabetes at least 12 times greater than that observed among native African blacks (12% and 1%, respectively) (21-25).

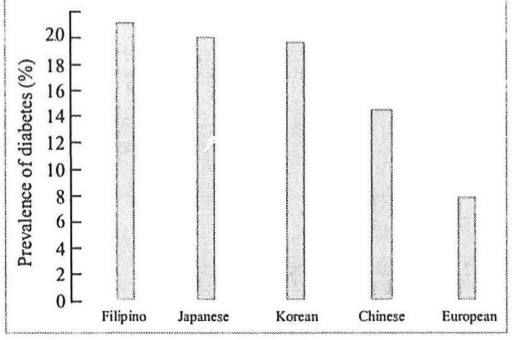
Mexican-Americans living in San Antonio have higher prevalence of type 2 diabetes than Hispanics living in Mexico. One of the most recent studies to have examined diabetes prevalence in Hispanics is the Mexico City Diabetes Study (26), in which 2,282 Mexicans age 35-65 years were examined during 1989-92. Participants were sampled from low-income "colonias" in Mexico City and the examination procedures were identical to those used in the San Antonio Heart Study. Diabetes was present in 12.8% of the men and 13.3% of the women. These rates were somewhat lower than the corresponding prevalence rates for Mexican Americans residing in the San Antonio Barrios (figure 4).

Figure 4. Diabetes in Hispanics



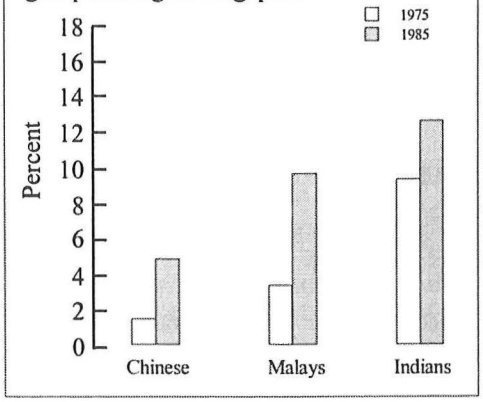
The Pima Indians of Arizona have the highest reported prevalence of type 2 diabetes (2). A study by Ravussin et al. (27) compared the prevalence of type 2 diabetes in Pima Indians living in Arizona to members of a population of Pima ancestry living in northwestern Mexico. In association with marked lifestyle differences, the two genetically-related populations had very different prevalence of diabetes. The Pima Indians living in Mexico were found to have a prevalence of 6% and 11%, for men and women respectively, as compared to the frequency of 54% and 37% reported in the Pima Indians living in Arizona.

Figure 5. Diabetes in various ethnic groups living in Hawaii



These studies clearly show that environmental factors play a significant role in the increasing prevalence of type 2 diabetes among the various populations of the world. The process of urbanization/westernization clearly is associated with a progressive increase in the prevalence of type 2 diabetes across all ethnic groups. However, the reported prevalence and the degree of changes in prevalence of diabetes appear to differ among various ethnic groups. This observation would suggest that there is an ethnic susceptibility to diabetes. Of interest are the epidemiological observations conducted in the multiethnic populations. Within the Hawaiian population, not only Japanese, Chinese, Koreans and Filipino have much higher prevalence of diabetes than the same ethnic group living in the country of origin, but also, the prevalence of diabetes is very different across the ethnic groups (28) (Figure 5). Similar observation has been done in Singapore where two separate evaluations of diabetes prevalence across ethnic groups have shown an increase for all ethnicity with maintenance of inter-ethnic differences in the two separate observations (13) (Figure 6). Less detailed subdivision of ethnic groups are available for the whole US population. However, the

Figure 6. Diabetes in various ethnic groups living in Singapore



changes in prevalence of diabetes, although involving all US ethnic groups, seem to have a different impact on various ethnicities (1,29) (Figure 7).

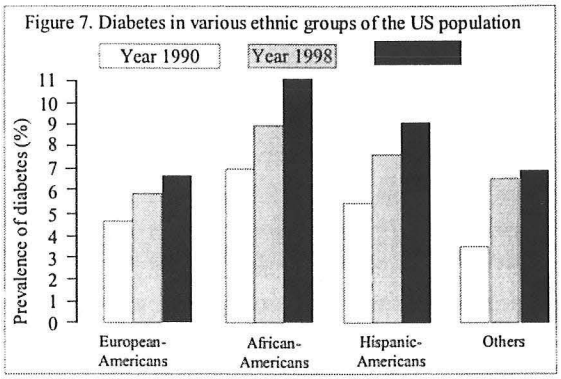


Figure 7. Diabetes in various ethnic groups of the US population

These studies taken together clearly show the impact of adoption of "western" life-style has on increasing prevalence of type 2 diabetes in our population, across all ethnic groups. However, these studies also point out another important issue: *a different predisposition of various ethnic groups to develop diabetes when exposed to similar environmental challenges*. As illustrated in table 1, epidemiological evidence is available to classify various ethnic groups on the basis of their susceptibility to develop diabetes. Among them, Hispanics, African-Americans and Asians appear to have much higher predisposition than individuals of European ancestry. Therefore, while the adoption of western life-style in countries outside US will seemingly produce a world-wide epidemic of diabetes in the future, the public health implications of these observations for the multiethnic US population are probably more urgent. The current data on immigration trends to US show that by the year 2030 over 50% of the population will include current minorities of non-European descent. The non-European descent population is going to be mainly represented by Hispanic- and Asian-origin ethnicities. Hence, if the impact of the western life-style on type 2 diabetes is larger in Hispanics and Asians than in European-Americans, in the near future we will witness an increase in the prevalence of diabetes in the US population of much larger proportion than what observed thus far. The public health implications are huge. The understanding of the mechanisms involved in the differential ethnic predisposition to the development of type-2 diabetes will help identifying areas of intervention to contain the foreseen epidemic of diabetes in our population.

Table 1. Ethnic susceptibility to diabetes

Susceptibility	Low	Medium	High	Very High
Prevalence	<10%	10-20%	>20%	>40%
Ethnic group	Bantu Melanesian European	Arab Asian Black Hispanics Polynesian	Asian-Indians	Micronesian (Nauru) Native American (Pima)

We will start discussing the available data on the impact that acquired factors related to urbanization and adoption of "western" life-style may have on inter-ethnic differences in prevalence of type 2 diabetes for the US population.

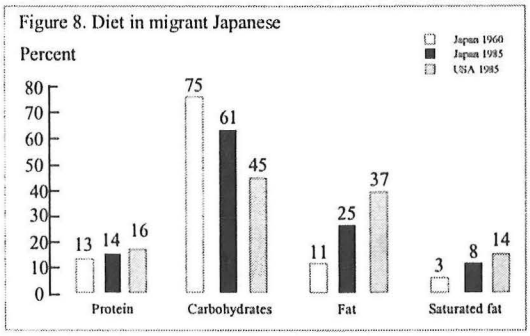
Relationship between "life-style" factors and ethnic differences in type 2 diabetes.

1. Diet and exercise.

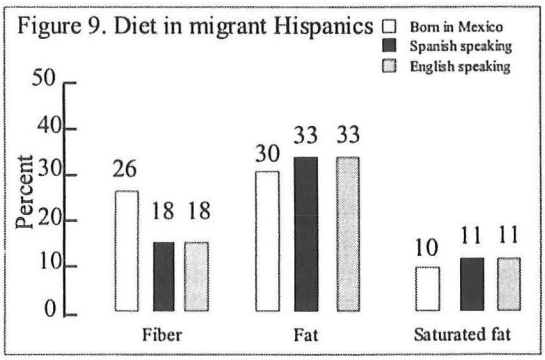
Reduced fiber intake and increased consumption of animal fats and processed carbohydrates are more commonly seen in US and constitute the main changes in dietary habits described in "westernized" societies. Both animal fats and carbohydrates have been associated with excessive predisposition to diabetes, mainly through development of obesity (30,31). Reduced fiber content in the diet has also been associated with increased predisposition to diabetes (32,33). Besides diet composition, higher daily energy intake, related to consumption of 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% (1). Level of physical activity is inversely related to the prevalence of type 2 diabetes (34). Reduced physical activity is observed in

association with the "urbanization and westernization" process. This seems to affect risk of diabetes independently of diet.

Migration of various ethnic subgroups to US has resulted in a change in dietary habits that is 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 (35). The Japanese-American diet was higher in calories, protein, fat and carbohydrates. The mean daily intake of fat in Japanese-American men was 32.4 gr, 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. Due to the doctrine of Buddhism introduced from China in the sixth century, Japanese people have been prohibited from consuming animal products with the exception of fish. Consequently, the traditional Japanese diet was extremely low in fat and cholesterol, high in carbohydrates, vegetable, fish and salt. The first immigrants (Isei) were young adults aged 20 to 30 years at their arrival. Further immigration was then prohibited by the Immigration Act of 1924. Since the age distribution of the Isei was clustered, their children (Nisei) and grandchildren (Sansei) constituted fairly discrete succeeding generations of Japanese-Americans. In addition, the Japanese-American population has maintained much homogeneity in terms of ethnicity. Intermarriages are only recently being observed with increasing frequency. A recent study conducted in Los Angeles indicated that food patterns and food choices have changed in succeeding generations of Japanese-Americans from traditional fare to a diet containing many complements and accessory foods that are higher in fat, sugar, sodium and calories (36). Figure 8 compares diet composition in Japan and in US. The data from Japan are shown for the year 1960 and 1985. The studies in migrant Japanese confirm that succeeding generation 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 are food comprising the 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.



Data from the third NHANES, conducted between 1988 and 1994, were used to compare energy, nutrients, and food intakes among 3 groups of Mexican-Americans (aged 25 to 64 years, 1449 women and 1404 men): those born in Mexico, those born in US whose primary language was Spanish, and those born in US whose primary language was English (37). Mexican-American born in Mexico ate significantly less fat and significantly more fiber, vitamin A, C, E, B-6, folate, calcium, potassium and magnesium than those born in US, regardless of the language spoken. Women and men born in Mexico were more likely than those born in US to have diets that contained less than 30% of fats and <10% of saturated fats and more than 25 g of fiber per day (Figure 9). Romero-Gwynn (38) found that Mexican-American immigrants living in California, who have become acculturated, had given up much of their traditional diet in exchange for one higher in fats and sugars. The changes include an increased consumption of flour tortillas, which are higher in fats than traditional corn



tortillas; a decreased use of lard but increased consumption of margarine, butter, vegetable oil, mayonnaise, salad dressing and sour cream; an increased consumption of sliced bread; an increased consumption of sugar-rich drinks and condiments; an increased consumption of ready-to-eat breakfast cereals; and a decreased consumption of chili and many traditional dishes with vegetables. The resulting diet is lower in fibers, beta-carotene, and specific nutrients provided by vegetables. Kunstadter (39) analyzed the dietary changes among Hmong refugees in Fresno, California. Compared with non-migrating Hmong in Thailand, an increase was seen in the intake of fat and salt. In a study comparing 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% of the daily caloric intake from fat (as compared to 22% in the Chinese living in China) and 48% of calories from carbohydrates (as compared to 62-68% in the Chinese living in China) (40). Boyce and Swinburn (41) have investigated the composition of the traditional Pima Indian diet of 100 years ago. Using ethno historic literature and traditional recepies, they estimated that the traditional diet consisted of about 70 to 80% carbohydrate, 8-12% protein; the current Pima Indian diet consists of about 47% carbohydrate, 35% fat, 15% protein, and 3% alcohol. Native Americans who participated in the Strong Heart Diet Study reported diets higher in fats than did participants in phase 1 of the third NHANES (42).

The level of physical activity has also been reported to be lower in ethnic groups living in their countries of origin as compared to the same ethnic groups living in US (40). Although, recent comparison of dietary trends among ethnic groups in the US has shown a trend towards a narrowing in the dietary differences (44), excess of caloric intake and reduced physical activity seems to be more accentuated in minorities as compared to the European-Americans (43). Dietary differences among ethnic groups (including both diet composition and caloric intake) and level of physical activity may contribute to the inter-ethnic differences in prevalence of type 2 diabetes observed in the US population.

2. Socio-Economic factors

There is an inverse relationship between socioeconomic status and prevalence of obesity and type 2 diabetes in the US population. Although the opposite may be true in developing Countries, higher than average rates of obesity have been linked directly with low income status within the US population. For example, in the NHANES III, socioeconomic status was significantly associated with BMI and physical activity (45). Although socioeconomic differences did not entirely explain interethnic differences in risk for diabetes, the racial/ethnic disparities in socioeconomic factors in the US suggest that at least part of the ethnic disparities in prevalence of type 2 diabetes may be related to socioeconomic factors.

One of the effects of socio-economic factors that potentially affect the prevalence of diabetes is low birth weight. Access to pre-natal care and malnutrition may be involved in increased risk for low birth weight, a condition directly associated with risk for type 2 diabetes. Recently Hales and Barker (46) proposed that intrauterine malnutrition leads to reduced birth size and to permanent changes in structure and function, which predisposes to type 2 diabetes, in the adult life.

Another example of how socio-economic factors may affect inter-ethnic differences in prevalence of diabetes is related to stress. Urbanization, migration and belonging to a minority group are associated with increased levels of stress. Stress has been associated with increased risk of type 2 diabetes (47). Migration, whether forced by poverty or persecution, leading to settlement in a different social, political and cultural context, might result in a long term defeat reaction regardless of previous health. In addition to migration stress,

not speaking the language of the majority culture may indicate a separation from the majority culture and create long-term acculturative stress.

3. Obesity

The most obvious consequence of western life style adoption and low socio-economic factors is the onset of obesity (48). However, there is evidence that environmental effects on the pathogenesis of obesity are modulated by genetic predisposition (49,50). Several studies have underscored the excessive prevalence of obesity in some ethnic groups, such as the Native-Americans, the Hispanics and the African-Americans as compared to European-Americans (51-54). Also, younger onset of obesity in minorities is a trend that appears to further increase the gap between European-Americans and other ethnic groups (55). Figure 10 illustrates the prevalence of BMI above the 85th percentile in children of various ethnic groups between 1986 and 1998 (55). The role that younger onset of obesity in minorities has in the increased prevalence of type 2 diabetes is emphasized by the observation that type 2 diabetes is more frequently seen in children of non-European ethnicity. Whereas the onset of type 2 diabetes is typically beyond the 3rd or 4th decade of life among European ethnicity, younger onset and childhood type 2 diabetes is now increasingly seen mostly in other ethnic groups. Among children in Japan, type 2 diabetes is already more common than type 1 diabetes, accounting for 80% of childhood diabetes (56). The incidence almost doubled between 1976-80 and 1991-95. Among Libyan Arabs <34 years of age, the annual incidence of type 2 diabetes is 19.6 per 100,000 for male patients and 35.3 per 100,000 for female patients, compared with incidences of type 1 diabetes of 9.4 and 8.5, respectively (57). Early onset of diabetes could certainly be one of the reasons explaining the epidemiological data of excessive diabetes in minorities of the US population. In North America, initial reports of a high frequency of type 2 diabetes in young patients came from the carefully studied Pima Indian population, in which children aged 5 years and over have been tested for diabetes for 30 years. The prevalence of diabetes for boys and girls of age 5 to 9 years, 10 to 14 years and 15 to 19 years are reported in figure 11, for different examination period since 1967 (58). For each sex the prevalence was higher in the older ages. Except for the younger group, in which only a few cases were recorded, the prevalence of diabetes increased two to threefold over the past 30 years. Diabetes in Pima Indians children is not associated with high titers of islet cells antibodies, insulin and C-peptide levels are not subnormal at diagnosis, and exogenous insulin is not required to prevent ketosis. Type 2 diabetes seems to be the prevalent form of diabetes in these children. Numerous instances of type 2 diabetes have been reported among native populations in Manitoba in the 5-14 years of age,

Figure 10: Prevalence rates of BMI greater than 85th percentile in children

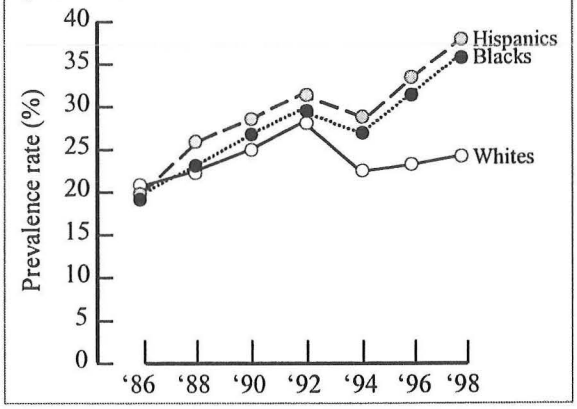
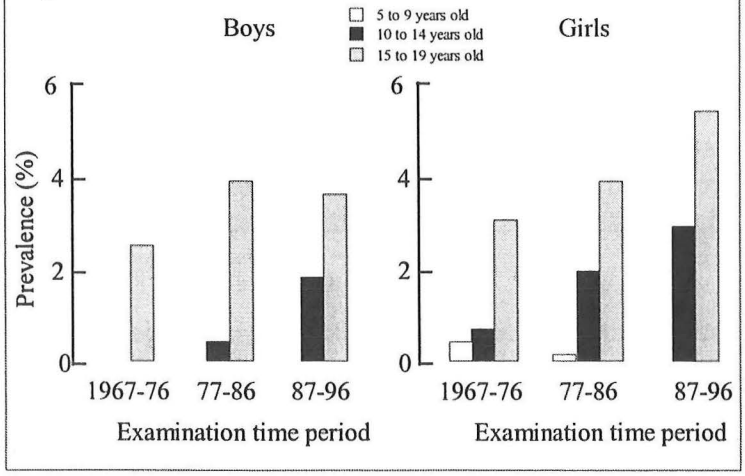


Figure 11. Prevalence of diabetes in Pima children



with a prevalence of 0.8 per 1000; 10-20% of new cases of diabetes in Manitoba were in the type 2 category (59). Increasing prevalence of childhood type 2 diabetes is not confined to the Native Americans. Similar reports are available for Hispanic-Americans and African-Americans (60).

In a report from Cincinnati, Ohio, type 2 diabetes accounted for 3 to 10% of all new cases of diabetes between 1982 and 1992 in the age group 10 to 19 year-old (61). Type 2 diabetes accounted for 33% of the new cases in the year 1994 for the same age group. In a clinic in Charleston, South Carolina, 97 African-Americans aged 0 to 19 years were diagnosed with diabetes; 46% of them had type 2 diabetes (60). Type 2 diabetes accounted for 47% of new cases of diabetes among Hispanic youths in Ventura, California (62).

Table 2. Prevalence of diabetes in children

Characteristics	Cincinnati, OH (n=54)	Charleston, SC (n=39)	Little Rock, AR (n=50)	San Antonio, TX (n=101)
Ethnicity (%)				
African-American	69	100	74	
Hispanic			2	83
White	31		24	
Mean BMI (kg/m_2)	38	30	35	
Acanthosis nigricans (%)	60	56	86	92

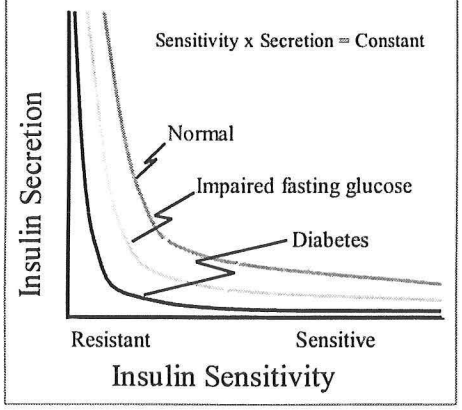
Table 2 is a summary of clinical characteristics of 578 North American children and adolescents at diagnosis of type 2 diabetes (60). Of note, the BMI of these children is often beyond 30 kg/m^2. Over 50% have acanthosis nigricans, a clinical manifestation of severe insulin resistance.

The problem of obesity has been so tightly associated with the increasing prevalence of diabetes observed in epidemiological studies to the point that the term ***"Diabesity"*** has been introduced by Shafrin, few years ago (63). Currently, intense investigations are underway to elucidate the details of the mechanisms that lead from the changes in lifestyle and tendency to obesity to the development of *diabesity*. Studies in different ethnic groups are of great value in this context. So, the question at this point is **"how does western life-style factors and obesity mechanistically affect the pathogenesis of "*diabesity*" in various ethnic groups?** We will first broadly discuss the pathophysiology of type 2 diabetes and observed ethnic differences in pathogenetic mechanisms. We will then specifically evaluate the effects of diet, exercise and obesity on the pathogenetic mechanisms of type 2 diabetes. Interethnic differences in predisposition to diabetes may have their roots in the interaction between life-style factors and/or obesity with pathogenetic pathways leading to type 2 diabetes.

Pathophysiology of *Diabesity*: ethnic differences.

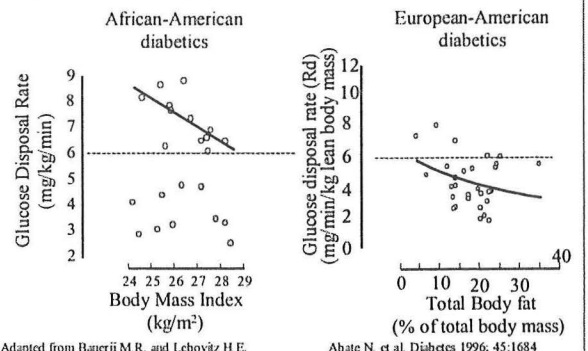
The pathogenesis of type 2 diabetes involves both insufficient insulin secretion and insulin resistance. As described by Bergman et al. (64) the relationship between insulin secretion and insulin resistance can be mathematically described as a hyperbole where the product of insulin resistance and insulin secretion is constant (Figure 12). Kahn et al. (65) 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 recently showed the large variability in the relationship between insulin sensitivity and insulin secretion in young European men and women (66). 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 normoglycemia if insulin sensitivity is maintained to match for the low beta cell function. The predominant mechanism leading to a shift of the constant relationship

Figure 12. Relationship between insulin action and β-cell function



between insulin resistance and beta-cell function, leading to IGT and diabetes could theoretically differ in various individuals or groups. Several cross-sectional studies have shown that either insulin resistance or reduced insulin secretion can be found in patients with IGT, a population at risk to develop type 2 diabetes and both insulin resistance and reduced insulin secretion can predict the onset of type 2 diabetes (67-69). Recently, Weyer et al. showed that both insulin resistance and beta-cell dysfunction characterize the progression from normal glucose tolerance to IGT and type 2 diabetes in Pima Indians (70). These subjects were characterized metabolically at different stages over an average of 5 years. The individuals who progressed to diabetes typically had a defective insulin response to progressively worsening insulin sensitivity. Those who did not progress to diabetes had an increase of insulin secretion in response to the worsening insulin resistance. It would seem that a failure of the beta-cell to adequately respond to insulin resistance will determine the progression of a given individual towards glucose intolerance. Although prospective data are lacking in different ethnic groups, it is possible that the progression to diabetes in various ethnic groups may be determined by a prevalent insulin resistance in some and by beta-cell dysfunction in others. In this regard, it is of interest that African-Americans with diabetes have been reported to frequently have relatively low rate of insulin resistance. In a study by Banerji, about 50% of African-American diabetic patients were insulin sensitive and the predominant mechanism leading to hyperglycemia appeared to be beta-cell dysfunction (71). A comparison of diabetic patients of African-American and European-American descent is illustrated in figure 13. In our study conducted on European-Americans with mild diabetes, severe insulin resistance was detected for any level of BMI (72). The UKPDS included type-2 diabetic patients from three major ethnic groups (73). Whereas most of the patients (82%) were whites, 10% were of Asian Indian origin and 8% 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. In a study in Japanese-Americans, Chen et al. (74) reported heterogeneity in the primary lesion leading to diabetes in this ethnic group. 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 groups. As shown in figure 14, Asian and Hispanic populations seem to have insulin resistance as the predominant mechanism leading to diabetes. Since these populations have the highest risk and rate of increase in prevalence of diabetes, understanding the mechanisms responsible for excessive insulin resistance in these populations will be of interest to identify targets of intervention to contain the growing epidemic of diabetes in the US population.

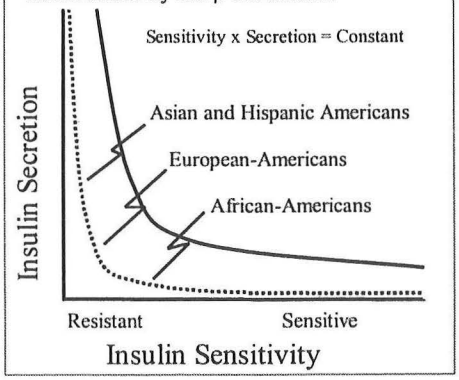
Figure 13. Ethnicity and insulin resistance in diabetes



Adapted from Banerji M.R. and Lebovitz H.E. Diabetes Care 1992; 10:1295

Abate N. et al. Diabetes 1996; 45:1684

Figure 14. Ethnicity and relationship between insulin sensitivity and β-cell function



So, at this point the question is: **what are the reasons for the apparent differences in the pathogenesis of type 2 diabetes in different ethnic groups? Why do Asians and Hispanics seem to develop more severe insulin resistance than subjects of European-descent? What is the relative impact that acquired and genetic factors have on these pathogenetic differences among ethnic groups?**

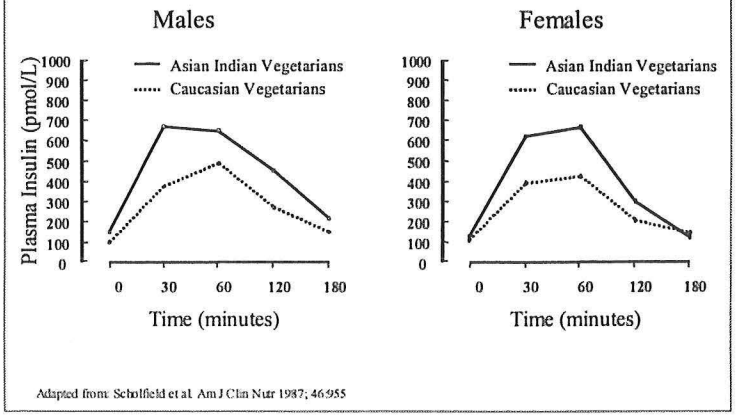
To answer these questions, we need to first examine the mechanisms whereby life-style factors and obesity have an impact on insulin sensitivity and beta-cell function. Second, we will have to examine how differences in lifestyle may affect insulin sensitivity and beta-cell function in different ethnic groups. Third, we will have to evaluate how genetic factors may modulate the impact of lifestyle factors on insulin resistance and beta-cell dysfunction.

1. Lifestyle factors and inter-ethnic differences in insulin resistance and beta-cell dysfunction. High fat diets have been implicated in the etiology of insulin resistance. Clinical studies have revealed adverse effects of experimental high fat, low-carbohydrate diets on glucose and insulin-mediated glucose metabolism in some (75,76) but not in all (77) 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. (78) 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 (79) 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. Several studies have identified dietary fat as a contributor to insulin resistance independent of obesity, but other studies do not support this. Nevertheless, it appears that all types of dietary fat may have an adverse effect on insulin sensitivity. Results are more consistent for an adverse effect of saturated fats. These effects may be enhanced among individuals with obesity or low level of physical activity.

Although early animal studies suggested a potential deleterious effect of dietary fat on insulin secretion, recent studies in human populations have failed to demonstrate either clinically or statistically significant effects.

The potential role of diet differences on insulin resistance of various ethnic groups has been evaluated in some studies. 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 (80). Total fat intake was inversely related to insulin sensitivity, but this association was not significant after adjustment for BMI and WHR. These findings were consistent on all ethnic groups studied. Some other studies have suggested that indeed high carbohydrate intake reduces insulin sensitivity in humans. Schonfeld et al. (81) compared a group of vegetarians of Asian Indian descent to a group of vegetarian of European descent. The Asian Indians had excessive insulin resistance despite similar dietary intake (Figure 15). In another study, diet composition did not contribute to the excessive insulin resistance of Asian Indians living in London (82). Therefore, the available data exclude dietary changes playing a significant role in the inter-ethnic differences in insulin resistance.

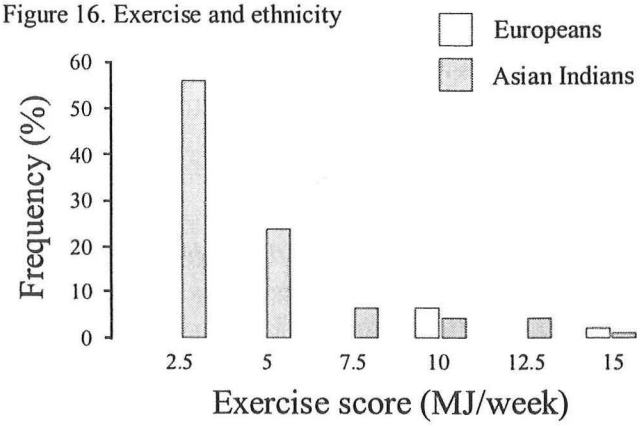
Figure 15. Diet and ethnic differences in insulin resistance



Adapted from: Scholfield et al. Am J Clin Nutr 1987; 46:955

In a study of Rosenthal et al. (83) sedentary life-style was associated with insulin resistance independent of generalized obesity 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 migrant to UK or US. However, in a study by Mc Keigue et al. (84) it was shown that leisure time activity but not working activity was decreased in migrant Asian Indians living in UK (Figure 16). Lack of leisure time activity did not explain the interethnic differences in insulin resistance between Asian Indians and Europeans.

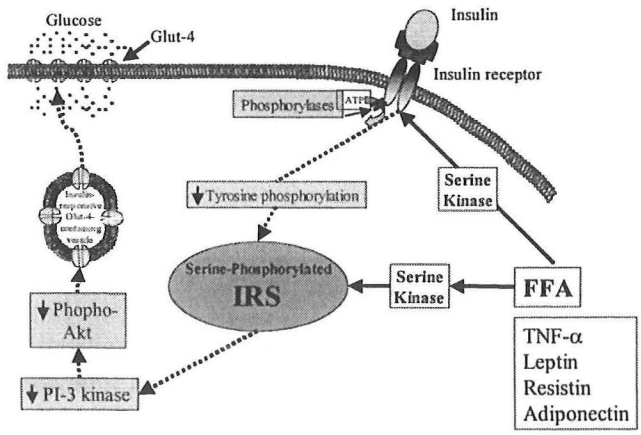
Figure 16. Exercise and ethnicity



By utilizing salivary cortisol measurements throughout the day, it has now been possible to show on a population basis that perceived stress-related cortisol secretion frequently is elevated in this condition (85). Socio-economic and psychosocial handicaps are probably central inducers of hyperactivity of the hypothalamic-pituitary adrenal (HPA) axis which leads to excessive secretion of cortisol in response to everyday stresses. Excessive daily secretion of cortisol has been associated with insulin resistance and may therefore predispose to diabetes.

2. Obesity /fat distribution and inter-ethnic differences in insulin resistance and beta-cell dysfunction. 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 (86-90). Insulin resistance is almost invariably present in subjects with BMI above 30 kg/m^2. 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 seem to play a role. Obese human subjects have decreased tyrosine kinase activity in skeletal muscle cells (91) and adipocytes (92). 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 intra-cellular insulin signaling: IRS-1 and regulatory subunit of the PI-3 kinase (93). This results in reduced mobilization of 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. Insulin resistance in obesity has in fact recently more specifically been related to intracellular accumulation of triglycerides in skeletal muscle cells (94).

Figure 17. Schematic representation of insulin action

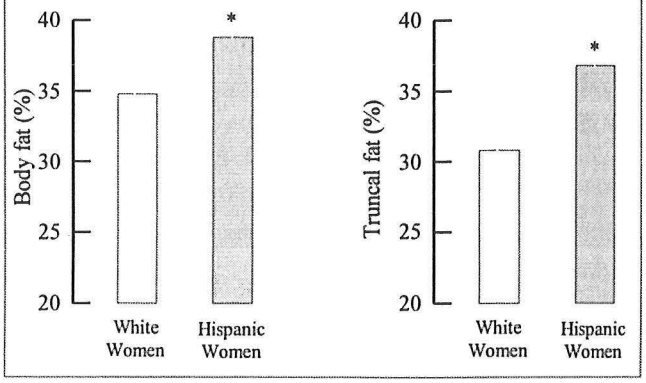


Excessive mobilization of free fatty acids from insulin resistant adipocytes may contribute to excessive

accumulation of triglycerides in the skeletal muscle cells. In a recent grand round the details of the mechanisms whereby fatty acids and intra-cellular accumulation of triglycerides in the skeletal muscle may induce insulin resistance were reviewed (95). Dr. Unger has also recently reviewed how triglycerides accumulation in the beta-cell may lead to beta-cell dysfunction and apoptosis, contributing to the progression from obesity to diabetes (96). Adipose tissue may affect insulin signaling in the skeletal muscle through alternative pathways. Adipose tissue has been shown to produce TNF-alpha, 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-alpha is a protein that is over-expressed in adipocytes of obese patients (97) and appears to have a paracrine function. In the same adipocytes or surrounding skeletal muscle cells, TNF-alpha may increase serine phosphorylation of the insulin receptor and also of IRS-1 (98) 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-signaling (99). Leptin is an adipocyte-derived hormone which increases in response to fat accumulation and reduces appetite through hypothalamic effect (100). 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 dysfunction (101). More recently, resistin (102) and adiponectin (103) have also been identified as adipocyte product 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% of the variability of insulin sensitivity is explained by obesity. Therefore, some individuals may be severely 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 (88-90). Therefore, it is conceivable that even in the absence of significant accumulation of total body fat, a preferential deposition of fat in the truncal/abdominal areas may be associated with changes in FFA flux and in production or action of TNF-alpha, leptin, resistin and adiponectin, with consequent onset of insulin resistance.

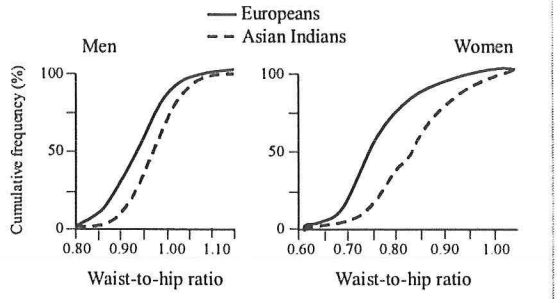
Ethnic groups, such as the Hispanics and the Asians that are more prone to develop abdominal obesity have more insulin resistance than those, like the African-Americans or White-Americans, who develop less abdominal obesity for similar degree of generalized adiposity. Ethnic differences in fat distribution have been considered a major contributor to the observed excessive prevalence of insulin resistance and diabetes in the Asian Indians, Japanese and Hispanics and Native Americans. Gilbert et al. (104) found a higher skinfolds thickness, particularly in the subscapular site, in adolescent Navajo Native Americans compared to Mexican-Americans, indicating a preferential truncal distribution of adipose tissue in the Navajos. Consistent with this observation is the finding that westernized Native Americans preferentially accumulate fat in the truncal adipose tissue compartments (105). Comparisons of anthropometric characteristics in Hispanics and Caucasians have shown that Hispanics tend to have increased subscapular skinfold thickness, whereas peripheral skinfolds are similar (106). Excessive truncal fat distribution has been reported in Hispanic women compared to white

Figure 18. Obesity and ethnicity



women of similar socio-economic status (107) (Figure 18). One study compared anthropometric variables in African Americans, Hispanics and European-American women (108). A higher waist-to-hip circumference ratio was reported for African-American as compared to the European Americans. The Hispanic women had the highest predilection for truncal distribution of fat. Lovejoy et al. (109) reported larger subcutaneous adipose tissue in middle-aged African-American women, as compared to European-American women of similar age and after adjustment for total body fatness. The effect of ethnicity on adipose tissue distribution has also been studied in Asian populations. Children of Tokelau Island have a higher subscapular skinfold thickness than the age-matched Europeans (110). Another study revealed a higher waist-to-hip ratio in Australian Aborigine women compared to Europeans (111). Asian Indians have been reported to have higher waist-to-hip ratio and thicker subscapular and suprailiac skinfolds as compared to Europeans with similar BMI (112) (Figure 19).

Figure 19. Fat distribution and ethnicity



Adapted from P.M. McKeigue et al. Lancet 1991; 337:382

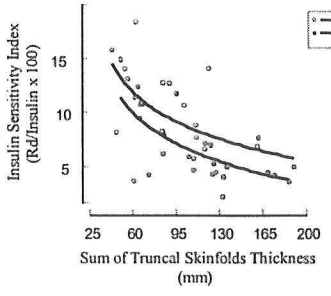
The case of the Asian Indians is of particular interest. This population has significantly more insulin resistance than European descent populations. The excessive prevalence of insulin resistance at population level has been observed despite the absence of excessive obesity. Since despite the absence 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. (113) recently proposed that excessive visceral adiposity in the Asian Indians could account for excessive insulin resistance in this ethnic group. Similar data were reported more recently by Raji et al. (114). However, these two studies lacked a direct comparison of the relationship between obesity and insulin resistance between 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 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 (115). 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 (Table 3). 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. As shown in figure 20, 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

Table 3. Ethnicity and fat distribution

	Asian Indians	Caucasians	p-Value
	Body composition		
Fat content (% of total fat)	20.3 ± 5.7	19.0 ± 6.6	0.51
Lean content (% of total fat)	79.7 ± 5.7	81.0 ± 6.6	0.51
	Body circumferences		
Waist (cm)	83.6 ± 6.7	89.4 ± 11.3	0.06
Hip (cm)	94.0 ± 5.9	98.0 ± 7.5	0.06
	Skinfold thickness		
Sum of truncal skinfolds (mm)	117.0 ± 37.0	92.4 ± 38.0	0.03
Sum of peripheral skinfolds (mm)	42.0 ± 13.0	42.0 ± 15.0	1.0

Chandalia et al. J. Clin. Endocrinol. Metab. 1999; 84: 2329

Figure 20. Relationship between insulin resistance and fat distribution in Asian Indians



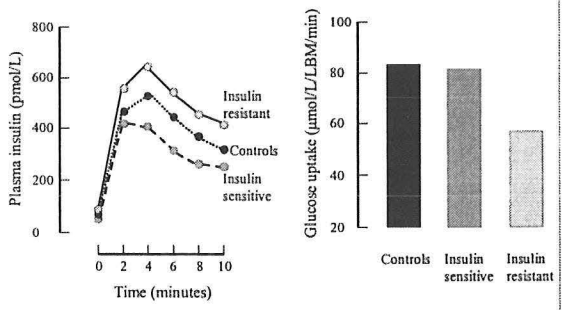
M. Chandalia et al. J. Clin. Endocrinol. Metab. 1999; 84: 2329-2335

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 genetic factors that may interact with obesity and fat distribution in determining excessive insulin resistance in Asian Indians is currently undergoing in our lab.

Similar data are available for the Hispanic (116) and the African-American populations (117). Neither obesity, nor fat distribution seems to completely account for the observed ethnic differences in insulin resistance. Excessive insulin resistance that we find in ethnic groups like the Asian Indians and the Hispanics is likely the result of an interaction between acquired factors, related to "western" life-style and genetic predisposition.

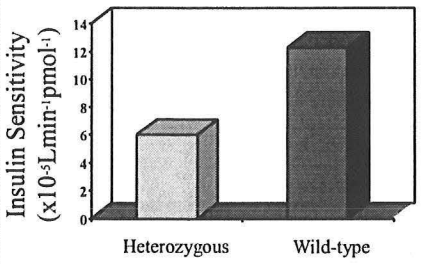
3. Genetic of insulin resistance and beta-cell dysfunction: ethnic differences. Defects in both insulin action and insulin secretion appear to be inheritable. The inheritability of insulin secretion and insulin action was recently evaluated by Vauhkonen et al. (118) in offspring of Finnish patients with type 2 diabetes (Figure 21). These investigators selected patients with different phenotypes of type 2 diabetes. One subgroup had elevated fasting C-peptide levels, reflecting insulin resistance, and the other subgroup had low fasting C-peptide levels, reflecting deficient insulin secretory capacity. Offspring of these patients were studied with hyperglycemic clamps and hyperinsulinemic clamps to measure insulin secretion and insulin action, respectively. Offspring of non-diabetic patients were included as controls. The offspring of probands with deficient insulin secretion phenotype of type 2 diabetes had impaired insulin secretion capacity, but normal insulin action, whereas the offspring of probands with insulin resistant phenotype had impaired insulin action but quite normal insulin secretion capacity. Thus the type 2 diabetic patients of this study mimicked the heterogeneity in the pathophysiology of type 2 diabetes that we have described for the whole population and we have also seen playing a major role in the inter-ethnic differences of type 2 diabetes.

Figure 21. Inheritance of insulin action and insulin secretion.



Vauhkonen et al. JCI 1998; 101:86-96

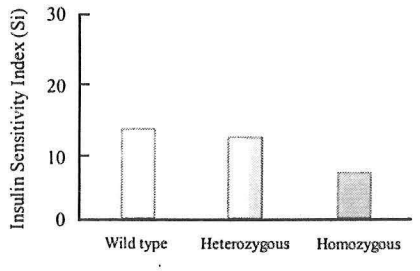
Figure 22. IRS-1 G972R Polymorphism and Insulin Resistance



From J.O. Clausen et al. Lancet 1995; 346:397

Genetic mutations of the insulin receptor have been associated with insulin resistance (119) but occur infrequently in the general population. Single nucleotide mutations of genes that are known to regulate insulin signaling and insulin secretion have been observed with a variable frequency in the general population and many of these genetic polymorphisms have been associated with increased frequency of type 2 diabetes. Polymorphisms of PTP-1B, LAR, PC-1, IRS, PI-3 kinase and virtually any of the genes involved in the expression of proteins that regulate insulin signaling (Figure 17) could impair glucose utilization in the skeletal muscle and contribute to insulin resistance (Figures 22 and 23). It is conceivable that a clustering of these polymorphisms may determine the genetic predisposition of some individuals to develop insulin resistance and therefore predispose to diabetes. The clustering of polymorphisms predisposing some ethnic groups to insulin resistance may have

Figure 23. PI-3 kinase M326I Polymorphism and Insulin Resistance



Adapted from T. Hansen et al. Diabetes 1997; 46:494

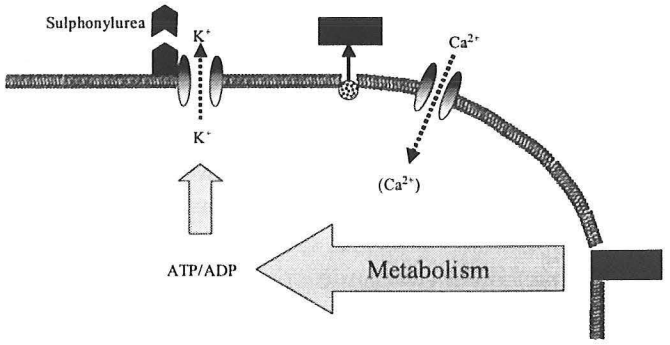
developed as a genetic advantage in populations such as the Hispanics and Asians. According to the thrifty genotype hypothesis (120), a predisposition to insulin resistance may have protected individuals during periods of food deprivation by reducing muscle utilization of glucose and favoring glucose utilization in organs, such as the brain, that operate through an insulin independent mechanism. The recent occurrence of excessive food availability and reduced physical activity constitute a rapid environmental change that interacts with the genetic predisposition to insulin resistance inducing a pathological decrease in glucose utilization. A genetic advantage has therefore become a genetic disadvantage and cause of disease. Multiple mutations of genes that individually are associated with small changes in insulin sensitivity, when combined may induce a significant reduction in insulin sensitivity. Therefore, the identification of individual mutations contributing to reduction in the biological effects of insulin will likely provide the key to the understanding of the genetic basis of insulin resistance.

Several mutations in the insulin receptor have been described (119). However, the low frequency of these mutations in the general population makes it unlikely that these mutations contribute significantly to the pathogenesis of diabesity in the whole population. IRS-1 was the first insulin-receptor substrate identified and the first to be found to have multiple natural polymorphisms (121-126). Polymorphisms of IRS-1 are significantly more common in type 2 diabetic patients than in controls and include the G972R (glycine 972arginine), S892G, G819R, R1221C, and A513P variants (121,122,126). Of these, the G972R polymorphism is the most common and has been studied most extensively. This polymorphism is found in Caucasian populations, with a prevalence of 5.8% in normal and 10.7% in type 2 diabetic patients, respectively. In Caucasian populations, obese carriers of this polymorphism show decreased insulin sensitivity during an oral glucose tolerance test, and an individual homozygous for the codon 972 mutation had a diabetic response to dexamethasone challenge. The polymorphism G972R does not occur in Pima Indians (127). Diabetic Asian Indians do not seem to have increased prevalence of G972R variant as compared to diabetic Caucasians (128). In African-Americans the allele frequency of G972R was not different between diabetics or insulin resistant non-diabetics and insulin sensitive non-diabetics (129). In Japanese type 2 diabetic patients, several additional polymorphisms have been described, including P190R, M209T, and S809F polymorphisms, and silent nucleotide variants Ll42 and G625 A804 (123). While the prevalence of each of these polymorphisms alone is not different between patients and healthy controls, the combined prevalence of these polymorphisms, along with the G972R polymorphism, is threefold greater compared with healthy controls (29.5 vs. 8.5%; $p < 0.05$). Insulin sensitivity in the carriers versus non-carriers of these polymorphisms has been reported to be decreased 29.5% in type 2 diabetics and 22% in healthy subjects. A common polymorphism of the p85-alpha subunit of PI3-kinase changes methionine in position 326 to isoleucine was observed with a prevalence of 31% in its heterozygous form and 2% in its homozygous form in a population of European descent. Although the frequency is not increased in diabetes, homozygous individuals do exhibit a 32% reduction in insulin sensitivity compared with wild type and heterozygous carriers in an intravenous glucose tolerance test (130). Other genetic variants associated with insulin resistance involve the Rad gene (Ras associated with diabetes) (131-133).

Although the mechanistic details of insulin secretion in the beta-cell are still incompletely elucidated, several beta-cell genes known to be involved in insulin secretion have been shown to be associated with certain forms of diabetes inherited in a dominant fashion: maturity onset diabetes of the young (MODY), and certain unusual forms of type 2 diabetes. Some of the genes involved in MODY, such as the glucokinase gene, have been tested for contribution in the development of type 2 diabetes by a gene-dosage mechanism. In other words, polymorphisms of the gene that reduce the levels of intracellular glucokinase activity to a various degree may cause increase in the threshold for glucose-stimulated insulin secretion. Polymorphisms of the glucokinase gene have been described in Caucasians, Hispanics and African-Americans and Japanese (134-139). Another

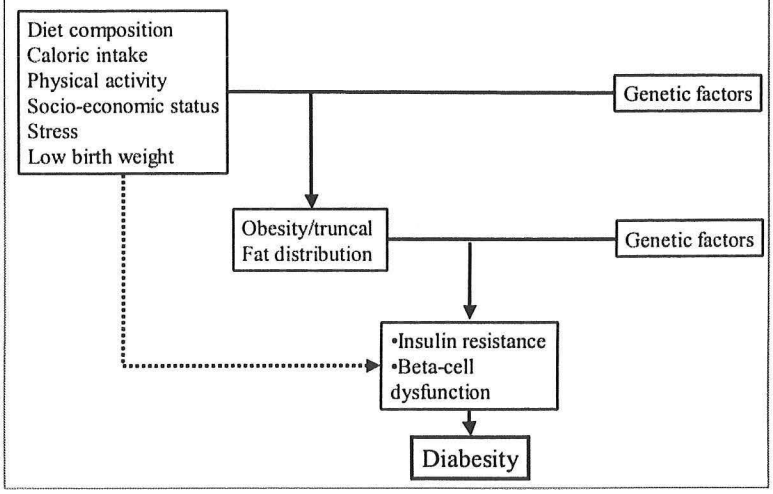
candidate gene for predisposition to beta-cell dysfunction is that regulating the beta-cell ATP-sensitive potassium (K_{ATP}) channel (Figure 24). This is a complex of two types of subunits, the sulphonylurea receptor (SUR1) and the potassium channel (Kir6.2). Polymorphisms in SUR1 have been found to be associated with type 2 diabetes in various Caucasian populations of northern Europe (140). However, the same gene has not been found to be associated with predisposition to diabetes in Mexican-Americans and in Japanese (141,142). Genetic abnormalities in the hepatocyte nuclear factor alpha and in the hepatocyte nuclear factor 4-alpha have also been associated with decreased beta-cell function. It has also been reported that polymorphism G972R of the IRS-1 gene may also be involved in defective insulin signaling besides insulin action. It has been shown that glucose-stimulated insulin secretion may be modulated by autocrine activation of the insulin signal-transduction pathway involving insulin receptor phosphorylation and its downstream phosphorylation cascade. In addition, genes involved in the regulation of beta-cell differentiation and apoptosis may affect beta-cell mass in islet cells and contribute to regulate beta-cell maximal secretory response potentials. Recently, Whiters et al. (143) reported that IGF-1 receptor couples with IRS-2 to mediate islet development during embryogenesis and promote beta-cell proliferation and survival during post-natal growth and in response to peripheral insulin resistance. Mice lacking IRS-2 develop type 2 diabetes. These mice are born with a 50% reduction in beta-cell mass and do not possess the mechanisms for a compensatory expansion of beta-cell in the presence of insulin resistance. The specific molecular targets of the IGF-1/IRS-2 signaling pathway in the beta-cell are poorly characterized.

Figure 24. Schematic representation of secretion



The above discussion on acquired and genetic factors affecting the pathogenesis of type 2 diabetes points out that type 2 diabetes is pathogenetically heterogeneous in different ethnic groups. The relative role that lifestyle-related factors have on the pathogenesis of *diabesity* in different ethnic groups seems to be variable and overall mediated through the effect of obesity. However, the degree of fat accumulation necessary to trigger excessive insulin resistance and beta-cell dysfunction seems to be extremely variable in the different ethnic groups. Genetic factors seem to modulate the relative impact of fat accumulation on predisposition of a given ethnic groups to type 2 diabetes. These considerations are of importance not only to the clinical investigators involved in the study of pathogenesis of type 2 diabetes, but also have an immediate practical implication in the evaluation of therapeutic and preventive strategies to control the growing epidemic of *diabesity* in our population and its associated morbidity and mortality.

Figure 25. Schematic representation of the pathogenesis of diabesity



Prevention and treatment of *Diabesity*.

The WHO classifies diabetes prevention into three levels: primary, secondary and tertiary. Primary intervention includes activities that prevent diabetes from developing. Secondary prevention includes activities, such as early detection of diabetes, prompt and effective management of diabetes, and also measures to halt its progression. Tertiary prevention includes measures undertaken to prevent complications and physical disabilities due to diabetes. **Diet, exercise, stress management and weight control are important at any level of diabetes prevention and treatment. Public health efforts should be encouraged to implement education at population level and encourage environmental changes to modify the identifiable "diabesogenic" factors of "western" societies. This could include promotion of workplace environments and communities infrastructures that promote healthy diet and physical activity and rewards weight maintenance.**

In this section we will discuss the implications of the current understanding of the heterogeneity in the pathophysiology of diabesity in various ethnic groups for treatment and prevention of this condition in the US population.

Diet, exercise, stress management and weight control. As discussed above, diet composition, caloric content and exercise are major variables that affect the pathogenesis of diabetes both directly and through promotion of fat accumulation. Therefore, modification in diet composition, caloric content and levels of exercise may not only be useful for glycemic control in patients with type 2 diabetes, but could also have a role in modifying the natural history of this disease and even prevent its onset. In fact, the impact of dietary and exercise intervention on treatment and prevention of diabesity have been proven in various studies. Diets low in fat are usually associated with modest loss of weight, which can be maintained as long as the diet is continued and if combined with aerobic exercise (144,145). Simply reducing the fat content of the diet can result in reduced energy intake and weight loss of 2-3 kg (146). Implementation of dietary changes usually requires frequent patient follow-up. In the UKPDS, before being randomized into study groups, subjects received 3 months of intensive nutrition therapy, which resulted in a 2% reduction of HbA1c and a mean 5% weight loss. The initial glucose response was reported to be more related to the decreased energy intake, with the decrease in body weight being a secondary response. Fasting plasma levels at 100 mg/dL were maintained only in individuals who continued a restricted energy intake; once caloric intake was increased, fasting plasma glucose levels increased, even when weight loss was maintained. A recent study conducted in mild diabetic patients revealed feasibility and effectiveness of high fiber diet (50 grams a day) in improving glycemic control and reducing 24 hrs plasma insulin levels (147). Although large amount of dietary fibers may have beneficial effects on diabetes management and even prevention, it is not known if such high levels of fiber intake can be maintained long term. However, studies in healthy subjects and those at risk for type 2 diabetes support the importance of including food containing carbohydrates from whole grains, fruits, vegetables, and low fat milk in the diet. Recent studies have provided preliminary evidence for reduced risk of diabetes with increased intake of whole grains and dietary fiber. In both the Nurse's Health Study (148) and the Iowa women's health study (149), increased intake of whole grain food was associated with significant reduction in incidence of type 2 diabetes. **Therefore, consumption of fibers and low fat diet is to be encouraged**. Among dietary fats it has been observed that saturated fats worsen insulin resistance and predispose to diabesity. On the other hand, monounsaturated fats tend to reduce risk for diabetes (149) and have also been shown to improve glycemic control in diabetics (150). Diets rich in carbohydrates and low in total fat also improve glucose tolerance compared to diets rich in fats (151). The total intake of saturated fat should not exceed 7-10%. Therefore, if saturated fats need to be replaced, they can be replaced with either carbohydrates or monounsaturated fats. There is, however, concern that when high mono-unsaturated fat diets are eaten "ad libitum" they may result in

increased energy intake and weight gain. Each individual's metabolic profile and need to lose weight will determine the dietary recommendations. For example, a diet in which 60-70% of energy is to be derived from carbohydrates and monounsaturated fat may emphasize carbohydrate intake for the patient to achieve weight loss and monounsaturated fat for the patient to improve plasma triglyceride levels or postprandial glycemia. Furthermore, an Asian patient may be more comfortable with a high carbohydrate diet, whereas a patient of Mediterranean descent may prefer a monounsaturated fat-containing diet. Fat intake should therefore be individualized and designed to fit ethnic and cultural backgrounds. Table 4 is a summary of current dietary recommendations for treatment and prevention of type 2 diabetes (152).

Table 4. Dietary recommendations

Nutrient	Recommended Intake
• Saturated fat calories	Less than 7% of total
• Polyunsaturated fat	Up to 10% of total calories
• Monounsaturated fat	Up to 20% of total calories
• Total fat	25–35% of total calories
• Carbohydrate	50–60% of total calories
• Fiber	20–30 grams per day
• Protein calories	Approximately 15% of total
• Cholesterol	Less than 200 mg/day
• Total calories (energy)	Balance energy intake and expenditure to maintain desirable body weight/ prevent weight gain

As discussed above, epidemiological studies have shown that the processes of migration and acculturation has resulted in a progressive increase of dietary fat, sugar and caloric content with a concomitant reduction of fiber content in the diet of various ethnic groups living in US. Modification of the acculturation process is possible by emphasizing the health advantages of various ethnic diets. This is mainly an educational issue that should be incorporated into available programs for treatment of *diabesity* but should also be incorporated into developing programs for population intervention and diabetes preventive strategies.

Regular exercise reduces risk for diabetes and improves management of diabetes through two main mechanisms: promotes weight maintenance and directly improves insulin resistance. Various mechanisms are possible to explain a direct effect of exercise on insulin resistance. Regular exercise increases the number of capillaries surrounding muscle fibers and also increases the skeletal muscle fiber composition that favors insulin-mediated glucose disposal (153). Bouts of exercise stimulate translocation of GLUT-4 to the plasma membrane and increase glucose transport in skeletal muscle (154). The signals that mediate exercise-induced GLUT-4 recruitment differ from those that mediate insulin-induced recruitment, in that insulin receptor expression and PI-3-kinase activity is not required for the exercise effect (155,156). Instead, activation of the 5-AMP-activated kinase may have a role (157). Exercise-induced production of NO and subsequent production of cyclic GMP may be involved in the regulation of glucose transport in muscle, independently of the effects of NO on vasodilatation (158). Bradikinin may also play a role in exercise-induced glucose transport, since it is released from muscle during exercise and, in cells expressing bradikinin receptors, it stimulates GLUT-4 translocation (159). Muscle has high levels of bradikinin receptors, and as with the glucose uptake stimulated by exercise, bradikinin-stimulated glucose uptake is not blocked by inhibitors of PI-3 kinase (159). The beneficial effect of exercise on insulin activity has recently been confirmed in the IRAS study (160).

Figure 26. Effects of exercise on glycemic control in diabetes

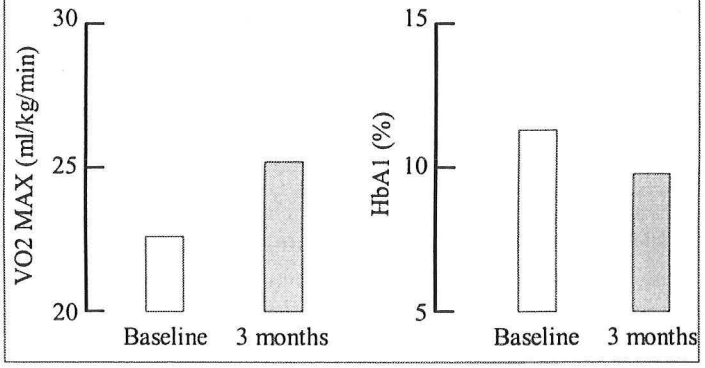


Figure 26 illustrates the results of a study by Schneider et al. (161) which included a lifestyle modification program based on education, nutritional recommendations and physical training. Subjects were asked to exercise 3-4 times a week. Patients with type 2 diabetes experienced an improvement in glycemic control and insulin requirements were significantly

reduced. Recent prospective studies have also shown that an active life-style not only improves glycemic control and insulin sensitivity in diabetic patients but also improves insulin sensitivity and prevents or delays the development of diabetes in non-diabetics who are at risk for developing the disease (162-165). Protection from diabetes appears to occur from moderate intensity activities, such as brisk walking, as well as from participation in vigorous physical activity. Diet and exercise seem to independently affect both risk and rate of progression of type 2 diabetes. In a Swedish non-randomized study (162), a 6-year intervention with diet and exercise advice resulted in 50% reduction in the incidence of diabetes in middle-aged men who volunteered to participate in the intervention group compared to those who were not willing to participate and thus served as controls. Pan et al. (163) reported on the marked decline in cumulative incidence of diabetes among subjects with IGT in the City of DaQing in China after 6 years of intervention with diet, exercise or combined diet and exercise. The incidence of diabetes was 67.7% in the control group compared with 43.8% in the diet group, 41.1% in the exercise group and 46% in the diet plus exercise group. **Interestingly, the intervention was equally successful in normal weight and obese individuals**. The Finnish Diabetes Prevention Study included life-style modifications to prevent diabetes in middle age IGT subjects and showed feasibility of life-style intervention in motivated individuals (164). A similar study was conducted in the US by the NIH and provided evidence for a 58% reduction in diabetes risk with exercise and diet (165). This study included multiple ethnicities and the final report will give information of the impact of diet and exercise in various ethnic groups.

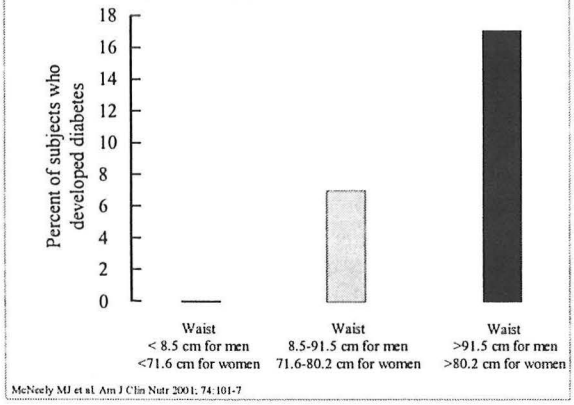
Table 5. Summary of studies on diabetes prevention

Study	Patient population	Intervention	Risk reduction
Finnish DPS	IGT	Diet and Exercise	58%
US DPP	IGT	Diet, Exercise	58%
		Metformin	31%
TRIPOD	Previous GDM	Troglitazone	56%

Although these clinical trials show feasibility and effectiveness of intervention focused on lifestyle changes, the question remains whether these strategies can realistically be implemented outside clinical trials setting. It is experience of the vast majority of health care providers that lifestyle changes are difficult to be maintained by patients. Also, the results of some dietary trials show that once the intervention period is over, body weight increases. Several modifiable obstacles to long lasting effective lifestyle modifications in various ethnic groups can be identified. For example, previous reviews of available diabetes education materials suggest that most literature is at a high reading level or is not culturally sensitive. Low literacy rates complicate diabetes care and education for many persons, including minorities. However, methods are available to present information in an interesting and appealing manner using skill-based workshops with practice, implementation and positive reinforcement. Traditional foods and medicines may decrease blood sugar levels and can be used to enhance acceptance of diabetes care. The ADA and NIH have developed cookbooks specifically targeted to some ethnic populations. However, the distribution of this available material is still insufficient. In addition, cookbooks and cooking classes should be developed at the local level for specific populations, using traditional flavors and forms but with reduced calories and fat content. Cultural attitudes towards obesity may also need to be addressed. Obesity is considered normal in many minority communities; in fact, it is often seen as not only acceptable but in some instances, preferable. Use of culturally and socio-economically appropriate diet and exercise intervention may enhance compliance.

Another important problem related to ethnicity is that goals of therapy for treatment and prevention of diabetes have to be tailored to specific ethnic group. For example, as discussed above for any level of BMI

Figure 27. Body fat distribution and risk of diabetes in Asians



some ethnic groups, such as the Asians, seemingly have a disproportionate increase in prevalence of type 2 diabetes. This not only suggests that more aggressive weight management strategies should be applied for minorities, but also that the goals for weight, diet composition and exercise should be different in the various ethnic groups. Since the risk of type 2 diabetes for any level of physical activity and obesity appears to be highest in Asians, individual of Asian origin should maintain BMI at lower levels than those of European origin and their daily physical activity should be higher. Perhaps even pharmacological intervention for weight control should be more encouraged in high-risk ethnic groups. Initiation of treatment for weight maintenance should be earlier than in European-Americans. The clinical suitability of a single definition of "normal" weight across ethnic groups remains unclear. The NHLBI guidelines (166) include waist circumference of 102 cm for men and 88 cm for women to identify high risk individuals with central obesity, but the cutoffs are based on white populations and may be inappropriate for Asians. Avoiding weight gain after reaching adult weight was proposed as an appropriate health goal, yet data on health consequences of weight gain in Asians are sparse. To determine the applicability of current reference ranges for overweight and central obesity to a high-risk Asian population, a recent study by McNeely et al. (167) was conducted in second and third generation Japanese-Americans. Among 240 non-diabetics Japanese-Americans, who were followed up for 5 years, diabetes risk was associated with BMI>25 kg/m2 at baseline, weight gain of more than 10kg and waist circumference above the third tertile. Therefore, the NHLBI definition for waist circumference above 88 cm for women and 102 cm for men was not appropriate for the Japanese-American population. A waist circumference above 91.5 cm for men and above 80.2 cm for women was enough to confer increased risk for diabetes (Figure 27). In our study on Asian Indians, excessive insulin resistance is seen with a BMI more than 22 kg/m_2 and waist circumferences larger than 80 cm. (115). Recently, experts from several Asian and Pacific countries recommended lower thresholds for BMI and waist circumference for Asians than for whites. Overweight, BMI $\geq$ 23; obese, BMI $\geq$ 25; high-risk waist circumference, $\geq$ 90 cm for men and $\geq$ 80 cm for women.

Metformin. Metformin improves glycemic control in monotherapy and in combination with other hypoglycemic agents. Although the liver is the primary site of action of metformin, in vivo studies indicate that metformin also increases glucose uptake into peripheral tissues (168). The UKPDS and other clinical trials have shown the effectiveness of metformin in improving glycemic control in patients with type 2 diabetes, both in monotherapy and in combination with other hypoglycemic agents (169). Metformin reduces HbA1c up to 2%. Recently, preliminary data of the DPP have shown that Metformin may also delays or prevents the onset of diabetes in individuals with IGT (165). A 31% reduction in the risk of diabetes was observed in the IGT patients treated with metformin for 5 yrs. Results on different ethnic groups are still unpublished and will shed light on whether ethnic differences are present in response to this pharmacological preventive modality.

Thiazoliendiones (TZDs). TZDs increase the disposal of glucose in peripheral tissues in animals and humans with insulin resistance, including subjects with type 2 diabetes (168). How these agents increase insulin-mediated glucose uptake is unclear. They appear to act as a ligand for a nuclear receptor, the peroxisomal proliferator-activated receptor gamma (PPAR-γ), augmenting the insulin action by enhancing insulin signaling at a post-receptor step (170). The effects of these agents in skeletal muscle may be direct or indirect. Treatment of insulin resistant rodents with thiazolidinediones restores the expression and translocation of GLUT-4 in

adipocytes (171). Thiazolidinediones also overcome the TNF-alpha-induced inhibition of insulin-stimulated glucose transport in adipocytes (172). In insulin resistant rats given high fat diets and insulin-deficient rats with streptozocin-induced diabetes, thiazolidinedione treatment increases insulin-stimulated glucose uptake in muscle (171). Rosiglitazone and pioglitazone are currently available TZDs in US. These two drugs reduce HbA1c by 1.5% when used in mono-therapy in type 2 diabetic patients. TZDs may also delay or prevent the onset of type 2 diabetes. The TRIPOD study (173) recently showed the beneficial effect of TZDs in prevention of diabetes in women who had history of gestational diabetes (GDM) and were therefore at high-risk for development of type 2 diabetes. The women enrolled in this study were of Hispanic ethnicity. They were assigned to either placebo treatment or to treatment with troglitazone, a TZD no longer available. Women who received the drug had a 56% reduction in the incidence of type 2 diabetes compared with women who received placebo during a median follow-up period of 30 months. Most importantly, protection from diabetes during troglitazone treatment was most closely related to the degree to which an increase in insulin sensitivity in the first 3 months on trial resulted in a reduction in the amount of insulin required to maintain stable glucose tolerance. In other words, reducing secretory demands placed on beta-cells by chronic insulin resistance greatly reduced the risk of deterioration to diabetes during a 30-month period (unpublished). Whether the results with troglitazone are generalizable to currently available TZDs and to all ethnic groups, remains an open question. However, the results of this study provide support for the concept that insulin resistance contributes significantly to the poor beta-cell function in subjects who develop diabetes.

Whether insulin secretory defects or insulin action defects are the predominant mechanisms leading to type 2 diabetes in a given individual or ethnic group, both the lifestyle and the pharmacological intervention studies discussed above provide rationale for focusing on insulin resistance and beta-cell rest when developing and testing strategies for prevention of type 2 diabetes. Several studies provide evidence that the approach aimed at high-risk individuals (for example those with IGT) may not be enough to prevent all cases of type 2 diabetes. Data from the UKPDS indicate that pancreatic beta-cell function is already substantially reduced at the time of clinical diagnosis of type 2 diabetes. Even at an earlier stage of IGT, beta-cell function is already impaired and intervention at this stage may be too late to prevent many cases of type 2 diabetes. So, the question at this point is: **when and how should intervention for prevention of diabetes begin?**

Screening and goals of prevention strategies. American Diabetes Association (ADA) recommendations are shown in Table 6. Screening in high risk minority individuals should probably be done earlier than 45, probably around 30 years of age. In fact, since the incidence of type 2 diabetes has been shown to be increasing in children and adolescents, screening and treatment has to be considered for children and adolescents (Table 7). This, again, should have a stronger emphasis in minority groups.

Table 6. Criteria for screening in adults

- All individuals of age 45 years and above (repeat every 3 years if normal)
- All individuals of age <45 years (repeat at intervals <3 years if normal) who:
  - have BMI $\geq$ 25 kg/m$_2$
  - have first degree relative with diabetes
  - are members of high risk population (e.g. African-American, Latino, Native American, Asian-American, Pacific Islander)
  - have delivered a baby weighing $\geq$9 lb or have Dx of GDM
  - have HTN
  - have HDL $\leq$ 35 mg/dL and/or triglycerides $\geq$ 250 mg/dL
  - have IGT or IFG on previous testing
  - have other clinical condition associated with insulin resistance (e.g. PCOS or acanthosis nigricans)

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Table 7:Criteria for screening in children

- Criteria
  - Overweight (BMI > 85th percentile for age and sex, weight for height >85th percentile, or weight >120% of ideal for height)

  plus

  - any of the following risk factors
    - Family history of type 2 diabetes in 1st or 2nd degree relatives
    - Race/ethnicity (e.g. African-American, Latino, Native American, Asian-American, Pacific Islander)
    - Signs of insulin resistance (Hypertension, dyslipidemia, PCOS,acanthosis nigricans)
- Age of initiation: age 10 yrs or at onset of puberty, if puberty occurs at younger age
- Frequency: every 2 years
- Testing: fasting plasma glucose preferred

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Since insulin resistance is associated with high risk for development of type 2 diabetes, the ADA recommendations for screening include patients with evidence of insulin resistance. Recent evidence from the NHANES III is available for a significant increase in the percentage of the US population manifesting clinical signs of insulin resistance (176). About 24% of the US population has been estimated to meet the criteria for the diagnosis **of the metabolic syndrome**, as defined by the ATP III (177). In fact, the same study revealed that the prevalence is significantly high even in young age groups and is higher in minorities. **Since the fundamental metabolic abnormality of the metabolic syndrome is insulin resistance, patients with the metabolic syndrome should probably be included in diabetes prevention programs.** All patients with high risk for diabetes, including patients with the metabolic syndrome, should be included in intervention with lifestyle modification. Although future developments in the understanding of the genetic basis of diabetes will allow focusing intervention based on genotype, we currently propose to maintain close follow-up on fasting and perhaps post-prandial glucose levels to identify individuals who may benefit from pharmacological intervention (Figure 29).

Figure 28. The metabolic syndrome and diabetes

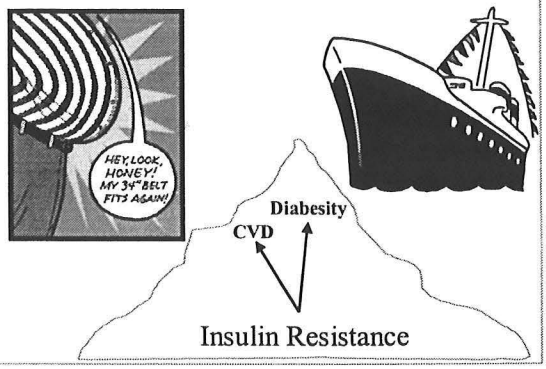
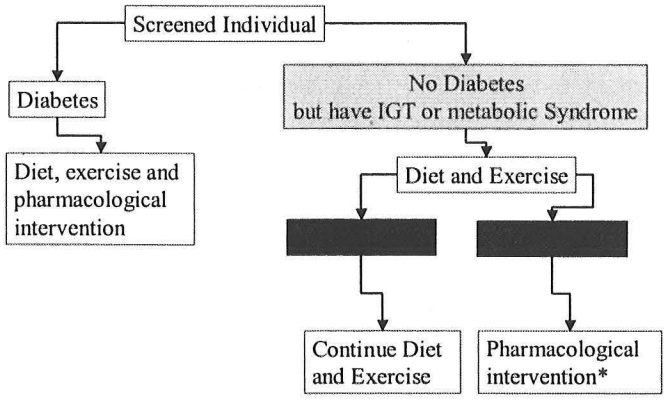


Figure 29. Algorythm for prevention of type 2 diabetes



* For children and adolescent there are no data supporting use of pharmacological intervention to prevent or delay type 2 diabetes

Table 8. Goals of Intervention

• Patient education	Increase motivation to engage and adhere to healthy behavior for lifetime
• Promote healthy diet	60-70% complex carb. and Mono.; 30 gr fibers
• Promote physical activity	Improvement in endurance, strength, flexibility and overall wellbeing
• Promote weight loss	5-10% of baseline
• Normalize lipids	Reduce LDL and TG; increase HDL
• Normalize glycemia	Maintain or decrease from baseline
• Normalize blood pressure	Maintain or decrease from baseline

As shown in table 8, goals of treatment should include compliance with low saturated fat and high fiber diet, 5% to 10% weight loss and regular exercise. Patient education and close follow-up by dietitians or nurses should be provided to assure long term adherence to primary prevention programs. Health care organizations and public health officials should be encouraged to support these programs with incentives both for the patients (such as premium cuts, etc.) and health care providers (such as reimbursement for education and frequent follow-up of these patients). Implementation of aggressive primary prevention program that take into account ethnic diversity will likely control the rampant epidemic of *diabesity* in the US population.

Conclusions.

The number of Asian-Americans and Hispanics living in US has increased rapidly since 1970. Asians and Pacific Islanders numbered 1.5 million in 1970, more than 3.7 million in 1980 and 7.3 million in 1990. Asians, Hispanics and Asian-Indians showed the greatest percentage change between 1980 and 1990 when compared with other major ethnic groups in the US. These ethnic groups appear to have a very high risk for type 2 diabetes which is accelerated by the adoption of the US lifestyle and the process of acculturation. While identification of interethnic differences in the pathophysiology of type 2 diabetes are being utilized by clinical investigators to better understand the mechanisms involved in the development of this disease, health care professional should familiarize with impact of ethnicity on type 2 diabetes. Understanding these premises will help refining treatment strategies and educational issues for each ethnic group which will lead to improved outcome. Understanding these premises will also help identifying better ways to prevent diabetes in the whole strata of the US population. Clearly, the growing epidemic of *diabesity* deserves urgent evaluation of potential impact on health resources and development of public health strategies to contain this increase.

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