Obesity, Diabetes and Cardiovascular Disease in Migrant South Asians

Nicola Abate and Manisha Chandalia

INTRODUCTION

South Asians have been reported to be at high risk for both diabetes and cardiovascular disease (CVD) (Hughes, 1989; Balarajan, 1991; Anand et al., 2000; Lee et al., 2001; Chandalia and Deedwania, 2001), two major causes of disability and mortality in western Countries. The incidence for diabetes and CVD is increasing also in developing Countries, including those in the South Asian region. Obesity and central fat distribution are important predictors of both diabetes and cardiovascular disease and appear to play a major pathogenetic role in these two disease entities. The growing "*westernization*" of South Asian Countries and adoption of "obesogenic" life-style may therefore contribute to the alarming increase in prevalence of diabetes and CVD. However, recent studies suggest that South Asians are at increased risk for any level of obesity and central fat distribution, when compared to European descent persons. It is possible that ethnic-related life-style factors, including diet, may explain some of the excessive risk. However, a major role may be played by genetic susceptibility. This review will summarize the data available on the complex interaction between environmental and genetic factors in the pathogenesis of diabetes and CVD with particular emphasis on the migrant South Asian population. The implications for diabetes and cardiovascular disease management and prevention will also be discussed.

Epidemiological Evidence for Ethnic Predispo-sition to Type 2 Diabetes and CVD in South Asians: A wealth of epidemiological data shows that the prevalence of diabetes and CVD in various ethnic groups is influenced by environmental factors (Zimmet et al., 1990; Toyota et al., 1976; Kitazawa et al., 1983; Kuzuia et al., 1992; Kawate et al., 1980; Fujimoto et al., 1987; Zhisheng, 1983; Tay et al., 1986; Cockram et al., 1993; Thai et al., 1986; Chou et al., 1992). This is also true for South Asians. It has been reported that South Asians living in rural areas of India have a prevalence of diabetes of about 2%. South Asians living in urban India like areas of Madras have a prevalence of diabetes of about 8%. South Asians migrated to UK or other "westernized" Countries, such as Singapore and Fiji, have about four times higher prevalence of diabetes compared to those living in India (Ramachandran et al., 1992; Dowse et al., 1990; McKeigue et al., 1989). Similarly, the prevalence of CVD in the migrant South Asian population is higher than in the same ethnic group living in the Country of origin (Chandalia and Deedwania 2001). This observation suggests that the life-style changes associated with the process of urbanization/westernization may largely explain the progressive increase in the prevalence of type 2 diabetes and CVD in this ethnic group. However, comparison with the prevalence of diabetes and CVD in South Asians and European descent persons living within the same environ-mental conditions, suggest that South Asians have unusual excess of both diseases, incomple-tely explained by life-style factors and related traditional risk factors. We will now review the data on the impact that acquired factors related to urbanization and adoption of "western" life-style may have on risk for type 2 diabetes and CVD in South Asians.

RELATIONSHIP BETWEEN "LIFE-STYLE" FACTORS AND RISK FOR TYPE 2 DIABE-TES AND CVD IN SOUTH ASIANS

***Diet and Exercise*:** Reduced fiber intake and increased consumption of animal fats and processed carbohydrates are the main changes in dietary habits described in "westernized" societies and adopted by migrant populations. Both animal fats and carbohydrates have been associated with excessive predisposition to diabetes, mainly through development of obesity (Hu et al., 2001; Meyer et al., 2001). Increased CVD risk factors, such as hypercholesterolemia and hypertension may be mediated by excessive saturated fat and salt intake adopted by migrant populations to western Countries. Reduced fiber content in the diet has also been associated with increased predisposition to diabetes (Meyer et al., 2000; Liu et al., 2000). Besides diet composition, higher daily energy intake, related to consumption of saturated fats and refined carbohydrates, predisposes to obesity, type 2 diabetes and CVD. For each kg of

weight gain it has been calculated that the risk for diabetes increases by about 4.5% (Mokdad et al., 2001).

There are no detailed data available on the changes in dietary habits in South Asians who migrate to western countries. However, studies conducted in other ethnic groups living in US have shown that changes in dietary habits of migrant populations are related to the process of *acculturation*. One study that compared the dietary content of similarly aged Japanese-American men living in Seattle with that of Japanese men in Japan showed that the Japanese-American diet was higher in calories, protein, fat and carbohydrates (Lands et al., 1990). 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. A recent study conducted in Los Angeles indicated that food patterns and food choices have changed in succeeding generations of Japanese-Americans from traditional diet to a diet containing many condiments and accessory foods that are higher in fat, sugar, sodium and calories (Kudo et al., 2000). The studies in migrant Japanese confirm that succeeding generations of immigrants maintain intake of food attached to their cultural identity longer than food that enhance the taste and palatability of basic foods. When new food is incorporated into diet of immigrants, they frequently include accessory food group, including sweets, snacks and soft drinks. Excess intake of accessory food may contribute to increased intake of fat, sodium, sugar and calories.

Other studies conducted in Asian populations include a comparison of dietary habits and physical activity between Chinese in North America and those living in China. Differences included higher meat and dairy products intake in the Chinese living in North America with about 35% 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) (Lee et al., 1994).

Reduced physical activity is observed in association with the "urbanization and westernization" process and seems to affect risk of diabetes and CVD independently of diet. The level of physical activity has been reported to be higher in ethnic groups living in their countries of origin as compared to the same ethnic groups living in US (Lee et al., 1994). Although, recent comparison of dietary trends among ethnic groups in the US has shown a trend towards a narrowing in the dietary differences (Popkin et al., 1996), excess of caloric intake and reduced physical activity seems to be more accentuated in minorities as compared to the European-Americans (Chronic Disease in minority populations, 1994).

Socio-Economic Factors: There is an inverse relationship between socioeconomic status and prevalence of obesity, type 2 diabetes and CVD. 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 (Winkleby et al., 1998). Although socioeconomic differences did not entirely explain interethnic differences in risk, 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 and CVD 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 et al. (1991) 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. A study by Yajnik et al. (2002) revealed that Indian babies tend to be smaller than European babies and have higher plasma insulin concentrations and a tendency towards central fat accumulation. This study suggested early onset of insulin resistance in relation to small weight and central fat accumulation. A study in over 1400 adults followed in Delhi, India, revealed that children at risk to become glucose intolerant as young adults often are at low birth weight and have rapid gain of BMI in early childhood (Bhargava et al., 2004). Taken together these data suggest that both genetic and nutritional factors involved in regulation of fetal growth, weight at birth and weight gain during early childhood, may affect susceptibility of migrant Asian Indians to insulin resistance, diabetes and CVD. Understanding the pathogenesis of these observations may help

identify area of intervention to prevent diabetes in this population.

Obesity: The most obvious consequence of western life style adoption and low socio-economic factors in migrant populations is the onset of obesity (Sundquist and Winkleby 2000). Prevalence of obesity is generally increased in persons who migrate to "western" Countries when compared to the population of their Country of origin. Studies conducted in South Asians migrated to UK have shown that there is a trend towards obesity and particularly towards accumulation of fat in the abdominal/truncal area in migrant South Asians when compared to the local Caucasian population. The tendency towards central fat distribution has been greatly emphasized as a cause of excessive predisposition towards diabetes and cardiovascular disease in migrant South Asians. Increased abdominal/truncal obesity associates with decreased biological activity of insulin and compensatory hyperinsulinemia, a condition often described as insulin resistance. Therefore, it has been proposed that insulin resistance, as a consequence of western life-style adoption may explain the excessive predisposition to diabetes and CVD of the migrant South Asian population.

There are several lines of evidence to support the notion that South Asians have excessive insulin resistance. For example, a sub-study of the UKPDS (1994) included a comparison of insulin resistance and beta-cell dysfunction in type-2 diabetic patients of South Asian (10% of the study population), European (82%) and Afro-Caribbean origin (8%). Insulin resistance was highest in the South Asians, followed by the European descent and by the Afro-Caribbeans. On the contrary, beta-cell function was best in South Asian diabetics and worse in the Afro-Caribbeans. The beta-cell function of European descent patients was between the two other ethnic groups. Studies in South Asians migrated to U.K. have shown excessive insulin resistance in South Asians even within the non-diabetics. It is therefore possible that excessive insulin resistance may explain the excessive risk for diabetes in migrant South Asians. Since insulin resistance has also been implicated in the pathogenesis of various cardiovascular risk factors, including dyslipidemia, hypertension and and micro-inflammation, this metabolic abnormality may also explain the excessive risk for CVD in migrant South Asians. Therefore, the understanding of the mechanisms that lead to excessive insulin resistance in migrant South Asians may elucidate pathways of intervention for prevention of both diabetes and CVD in this population. Again, life-style factors and obesity/fat distribution come into play in the understanding of the pathogenesis of insulin resistance. We will first describe the links between diet and exercise with insulin resistance. We will then evaluate the role of obesity and fat distribution in the pathogenesis of insulin resistance.

RELATIONSHIP BETWEEN OBESITY FACTORS AND GENES IN THE PATHOGENESIS OF INSULIN RESISTANCE

Role of Diet and Exercise: 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 (Mayer-Davis et al., 1997). 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. (1987) compared a group of vegetarians of South Asian descent to a group of vegetarian of European descent. The South Asians had excessive insulin resistance despite similar dietary intake. In another study, diet composition did not contribute to the excessive insulin resistance of South Asians living in London (Sevak et al., 1994). Therefore, the available data exclude dietary changes playing a significant role in the inter-ethnic differences in insulin resistance.

In a study of Rosenthal et al. (1983) 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 McKeigue et al. (1992) it was shown that leisure time activity but not working activity was decreased in migrant South Asians living in UK. Lack of leisure time activity did not explain the interethnic differences in insulin resistance between South Asians and Europeans.

Role of Obesity/Fat Distribution: Studies per-formed in various ethnic groups and in both genders have shown that increasing body fat

content is linearly and inversely related to insulin resistance. (Bogardus et al., 1985; Bonadonna et al., 1990; Abate et al., 1995; Goodpaster et al., 1997; Karter et al., 1996). 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 under-stood. Defective insulin signaling in both the skeletal muscle and the adipocyte seems to play a role. Obese human subjects have decreased tyrosine kinase activity in skeletal muscle cells (Caro et al., 1987) and adipocytes (Olefsky, 1976). 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 (Goodyear et al., 1995). As a consequence obesity associates with 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 (Pan et al., 1997).

Excessive mobilization of free fatty acids from insulin resistant adipocytes may contribute to excessive accumulation of triglycerides in the skeletal muscle cells. Adipose tissue may affect insulin signaling in the skeletal muscle through alternative pathways. Adipose tissue has been shown to produce 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 (Hotamisligil et al., 1995) 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 (Kanety et al., 1995) 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 (Peraldi and Spiegelman, 1998). Leptin is an adipocyte-derived hormone which increases in response to fat accumulation and reduces appetite through hypothalamic effect (Friedman, 2000). 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 (Unger and Zhou, 2001). More recently, resistin (Steppan et al., 2001) and adiponectin (Yamauchi et al., 2001) 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 relation-ship 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, insulinmediated glucose disposal is reduced, independent of overall degree of adiposity (Abate et al., 1995; Goodpaster et al., 1997; Karter et al., 1996). 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.

We have recently reported on the differences in plasma NEFA concentrations, plasma NEFA suppression during hyperinsulinemia, leptin and adiponectin concentrations in a group of non-diabetic migrant South Asians living in Dallas and compared to European descent non-diabetics of European descent matched for age and body composition (Abate et al., 2004). In that study we observed that plasma concentrations of adipose tissue metabolites leptin and adiponectin are higher and that of adiponectin is lower in insulin-resistant South Asians compared with more insulin sensitive Caucasians. These differences may contribute to the excessive prevalence of type 2 diabetes and CVD of non-obese Asian Indians. Since despite the absence of obesity, the South Asian population seems to be characterized by a tendency towards truncal accumulation of fat, some investigators have proposed that the

excessive insulin resistance in South Asians could be explained by an abdominal fat distribution which, in turn, may be genetically determined. Banerji et al. (1999) recently proposed that excessive visceral adiposity in the South Asians could account for excessive insulin resistance in this ethnic group. Similar data were reported more recently by Raji et al. (2001). 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 South Asians we recently performed hydro densitometry, skinfolds measurements and euglycemic-hyperinsulinemic clamps in 21 healthy South Asian men and 23 Caucasian men of similar age and body fat content (Chandalia et al., 1999). Despite similar total body fat content, South Asians had higher truncal adiposity than Caucasians. In both South Asians 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, South Asians still had excessive insulin resistance compared to the Caucasians. For any level of truncal skinfolds thickness South Asians 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 South Asians 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 South Asians is currently undergoing in our lab. We recently reported that a polymorphism of ENPP1, X121Q, is associated with excessive insulin resistance is South Asians living in Dallas and explains almost entirely the ethnic differences in insulin resistance between the Caucasians and the migrant South Asians of our cohort (Abate et al., 2003).

TRADITIONAL AND NON-TRADITIONAL CVD RISK FACTORS IN SOUTH ASIANS

The increased risk for CVD in migrant South Asians is partly but not entirely explained by high prevalence of type 2 diabetes. High prevalence of insulin resistance may also contribute to the excessive risk. No conclusive evidence is available in regard to the role of other traditional risk factors, such as hypercholesterolemia, hypertension and smoking. Some metabolic abnormalities, such as pro-inflammatory state and hyperhomocysteinemia have recently been linked to excessive CVD risk independently of traditional risk factors. These conditions are also indicated as non-traditional risk factors and their presence may suggest the need of a more aggressive treatment protocols for CVD risk reduction. We have observed that migrant South Asians living in Dallas tend to have both a pro-inflammatory state and increased plasma concentrations of homocysteine, when compared to the local population of European descent. Elevation of plasma hs-CRP concentrations are considered a manifestation of a pro-inflammatory state. Plasma hs-CRP concentrations are often elevated in prediabetes and diabetes. In a comparison of nondiabetic migrant South Asians and Caucasians of similar age and BMI, plasma hs-CRP was significantly higher in the South Asians in concomitance with excessive insulin resistance (Chandalia et al., 2003a). In another comparison of the two ethnic groups living in Dallas, migrant South Asians had significantly increased plasma homocysteine concentrations despite normal plasma folate (Chandalia et al., 2003b). Lower plasma concentrations of vitamin B-12 and lower insulin sensitivity partly explained this finding but only partially explained the ethnic differences described. Whether supplementation with vitamin B-12 may reduce ethnic differences in plasma homocysteine concentrations is currently being investigated.

PREVENTION OF DIABETES AND CVD IN MIGRANT SOUTH ASIANS

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 susceptible individuals, such as migrant South Asians. 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 (Lichtenstein et al., 1994; Carmichael et al., 1998). Simply reducing the fat content of the diet can result in reduced energy intake and weight loss of 2-3 kg (Sheppard et al., 1991). 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 (Chandalia et al., 2000). 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 (Liu et al., 2000) and the Iowa women's health study (Meyer et al., 2000), 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 hyperlipidemia and therefore increase risk for both diabetes and CVD. On the other hand, monounsaturated fats tend to reduce risk for diabetes and CVD (Meyer et al., 2000) and have also been shown to improve glycemic control in diabetics (Garg et al., 1988). Diets rich in carbohydrates and low in total fat also improve glucose tolerance compared to diets rich in fats (Simpson et al., 1979). 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 monounsaturated 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, South Asian patients may be more comfortable with a high carbohydrate diet, whereas a patient of European descent may prefer a monounsaturated fat-containing diet. Fat intake should therefore be individualized and designed to fit ethnic and cultural backgrounds (Franz et al., 2002).

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.

Regular exercise reduces risk for CVD and diabetes. It also 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 (Utriainen et al., 1996). Bouts of exercise stimulate translocation of GLUT-4 to the plasma membrane and increase glucose transport in skeletal muscle (Thorell et al., 1999). 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 (Wojtaszewski et al., 1999; Lund et al., 1995). Instead, activation of the 5-AMP-activated kinase may have a role (Hayashi et al., 1998). 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 (Young et al., 1997). 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

(Kishi et al., 1998). 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 (Kishi et al., 1998). The beneficial effect of exercise on insulin activity has recently been confirmed in the IRAS study (Mayer-Davis et al., 1998).

A study by Schneider et al. (Schneider et al., 1992) 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 (Eriksson and Lindgarde, 1991; Pan et al., 1997; Tuomilehto et al., 2001; NIDDK). 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 (Eriksson and Lindgarde, 1991), 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. (1997) 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 (Tuomilehto et al., 2001). A similar study was conducted in the US and provided evidence for a 58% reduction in diabetes risk with exercise and diet (NIDDK). Mild to moderate exercise and weight loss of 5-15% of body weught have been shown to significantly reduce risk for CVD. Goals of treatment in various ethnic groups, such as the South Asians, not included in these studies have to be identified. Since the risk of type 2 diabetes and CVD for any level of physical activity and obesity appears to be highest in South Asians, individuals of this ethnic group 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 those of European descent. The clinical suitability of a single definition of "normal" weight across ethnic groups remains unclear. The NHLBI guidelines (1998) 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 South Asians. Avoiding weight gain after reaching adult weight was proposed as an appropriate health goal, yet data on health consequences of weight gain in South 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. (2001) 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/m^2 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. In our study on South Asians, excessive insulin resistance is seen with a BMI more than 22 kg/m^2 and waist circumferences larger than 80 cm. (Chandalia et al., 1999). 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. Whether a similar approach should be used for migrant South Asians remains to be evaluated.

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 (Inzucchi et al., 1998). 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 (UKPDS, 1998). Metformin reduces HbA1c up to 2%. In the UKPDS, the obese subgroup treated with metformin was the only group that derived benefit for prevention of CVD. Recently, the DPP has provided evidence that Metformin may also delays or prevents the onset of diabetes in individuals with IGT (NIDDK). 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 (Inzucchi et al., 1998). 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-^{r}), augmenting the insulin action by enhancing insulin signaling at a post-receptor step (Lehmann et al., 1995). 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 (Hofmann et al., 1991). Thiazolidinediones also overcome the TNF-alpha-induced inhibition of insulin-stimulated glucose transport in adipocytes (Szalkowski et al., 1995). 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 (Hofmann et al., 1991). 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 (Azen et al., 1998) 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. 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 TZDs may also independently reduce CVD risk is still controversial but clinical trials are undergoing to test this hypothesis.

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 in the South Asian population begin*? Similarly, there is abundant evidence that atherosclerosis start in early childhood and progress rapidly in high risk individuals. Early evaluation and treatment of dyslipidemia and hypertension should be performed. In analogy to diabetes prevention, the question remains on *when and how should intervention for CVD begin in the migrant South Asian population.*

Screening and Goals of Prevention Strategies: The American Diabetes Association (ADA) (2004) and the NCEP-ATP III (2001) give recommendation for diabetes and cardiovascular risk factors screening for the US population.

Screening for diabetes in migrant South Asians should be done earlier than 45 year of age suggested for the European descent population. Because of the earlier onset of type 2 diabetes in migrant South Asians, screening should begin at around age 30 years. Screening for cardiovascular risk factors, such as dyslipidemia and hypertension should be performed in the pediatric population at 20 years. Goals of treatment should include compliance with low saturated fat, low sodium and high fiber diet, 5% to 10% weight loss (in overweight individuals) and regular exercise. Other important goals of treatment should include: blood pressure≤120/80 mm Hg; LDL-cholesterol<100 mg/dL; non-HDL-cholesterol<130 mg/dL (for patients with plasma triglycerides>200 mg/dL); HbA1c<7% (for the diabetics). Patient education and close follow-up by dietitians or nurses should be provided to assure long term adherence to primary prevention programs.

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KEYWORDS Type 2 Diabetes. Cardiovascular Disease. Ethnicity. Insulin Resistance. Obesity. Fat Distribution. South Asians

ABSTRACT South Asians are at increased risk for type 2 diabetes and cardiovascular disease. Although life-style changes, including increased caloric intake and decreased physical activity, appear to significantly contribute to the

heightened disease risk of migrant South Asians, genetic susceptibility appears to be particularly important in this population. More specifically, genetic susceptibility to insulin resistance and other non-traditional risk factors may play a major mechanistic role in predisposition to both diabetes and cardiovascular disease in migrant South Asians. Therefore, the understanding of the interactions between life-style, obesity and genetic variables in the pathogenesis of insulin resistance is of importance in defining parameters of intervention for disease prevention in this population. In this review we discuss pathogenesis of non-traditional risk factors in migrant South Asians. We also discuss recent findings from clinical trials to prevent type 2 diabetes in various populations, and identifiable criteria for screening and intervention for risk reduction in migrant South Asians.

Authors' Address: **Nicola Abate and Manisha Chandalia** M.D., U.T. Southwestern Medical Center, 6011Harry Hines Blvd., Dallas, Texas 75390-9169, USA
Telephone: 214 648 8367*; Fax:* 214 648 8364 ; *E-mail:* Nicola.Abate@UTSouthwestern.edu

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