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Pathogenesis of type 2 diabetes and cardiovascular disease in South Asians: effects of dietary interventions on metabolism and cardiovascular function

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2 Pathogenesis of type 2 diabetes in South Asians

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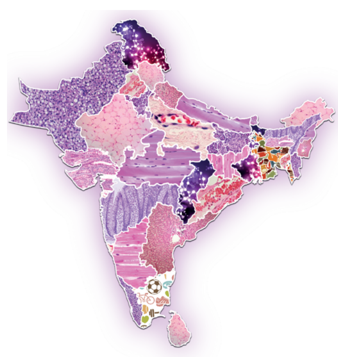

ABSTRACT

The risk of developing type 2 diabetes is exceptionally high among both native and migrant South Asians. Type 2 diabetes occurs more often and at a younger age and lower BMI, and the risk of coronary artery and cerebrovascular disease and renal complications is higher for this ethnicity compared to people of white Caucasian descent. The high prevalence of diabetes and its related complications in South Asians, which comprise one fifth of the total world's population, poses a major health and socioeconomic burden. The underlying cause of this excess risk, however, is still not completely understood. Therefore, gaining insight in the pathogenesis of type 2 diabetes in South Asians is of great importance. The predominant mechanism in this ethnicity seems to be insulin resistance rather than impairment in β-cell function. In this systematic review we describe several possible mechanisms that may underlie or contribute to the increased insulin resistance observed in South Asians.

INTRODUCTION

Worldwide the prevalence of type 2 diabetes increases, particularly in South Asian countries and especially in India, which currently has the highest global number of diabetes patients, with an estimated prevalence of up to 16.8% in urban areas.[1-4] Similar prevalence rates have also been reported in migrants of South Asian descent (India, Pakistan, Bangladesh, Nepal and Sri Lanka) in the United States of America (USA), Canada and various European countries.[5-8] In the Netherlands, South Asians mostly consist of Hindustani Surinamese who migrated from Surinam, a former Dutch colony in South America, and whose ancestors came from the Indian subcontinent about a century ago. Hindustani Surinamese have the highest type 2 diabetes prevalence of all ethnic minorities living in the Netherlands.[9] An age-standardized prevalence rate of type 2 diabetes of 26.7% for this group has been reported, compared to 5.5% in ethnic Dutch (**Table 1**).[10]

In addition to the increased prevalence, South Asians develop diabetes at a much younger age than white Caucasians and have an increased incidence of retinopathy, microalbuminuria and end-stage renal disease.[11-13] Furthermore, South Asians have an increased risk of developing coronary artery and cerebrovascular disease, and a 50% higher age-adjusted mortality rate from coronary heart disease.[8]

Uncovering the underlying mechanisms involved in the higher prevalence of type 2 diabetes in South Asians is very relevant, as they represent over 20% of the world's population. In this review we discuss the available literature on potential pathophysiological mechanisms responsible for the increased prevalence of type 2 diabetes in South Asians as compared to white Caucasians.

Table 1. Prevalence of T2DM in South Asians and white Caucasians

	Prevalence of T2DM	*References*
Rural India	3.0 - 8.3 %	2
Urban India	10.9 - 14.2 %	2
South Asians (Dutch)	26.7%	10
white Caucasians (Dutch)	5.5%	10

METHODS

The literature was searched using international databases: PubMed (1949 to July 2013), EMBASE (OVID-version, 1980 to July 2013), Web of Science (1945 to July 2013), and the Cochrane Library (1990 to July 2013). Terms used were 'South Asian' OR 'Indo Asian' combined with several keywords related to diabetes and its risk factors (i.e. type 2 diabetes mellitus, obesity, metabolic syndrome, insulin resistance, insulin secretion, body fat, liver fat, skeletal muscle, mitochondrial dysfunction, endothelial dysfunction, adipokines, inflammation). References were limited to studies in humans, written in English or Dutch. See the Supplementary Methods online for the complete literature search.

TYPE 2 DIABETES MELLITUS IN SOUTH ASIANS

Pathogenesis

Type 2 diabetes mellitus is a chronic, multifactorial disease characterized by a combination of insulin resistance and impaired insulin secretion (**Figure 1**).[14] The predominant mechanism, however, appears to be different in various ethnic groups.

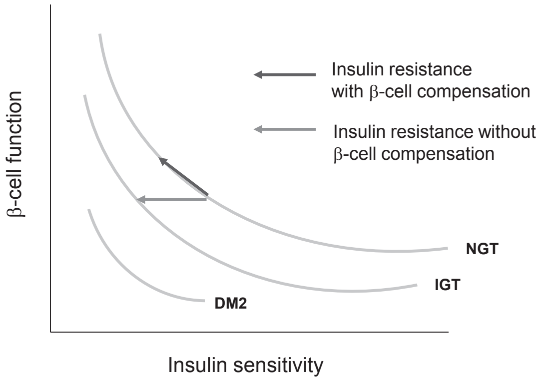

Figure 1. The relation between insulin sensitivity and β-cell function in type 2 diabetes. β-cell function adapts to insulin resistance in order to maintain glucose tolerance normal (derived from thesis I.M. Jazet, 2006, chapter 1, page 25).

Multiple studies have repeatedly shown that South Asians have higher fasting insulin concentrations compared to other ethnic groups regardless of age, gender or BMI, suggesting a higher rate of insulin resistance in this population.[15-25] Already in neonates fasting insulin levels are markedly higher compared to white Caucasian neonates,[26;27] and fasting insulin remains higher in school children[28;29] and teenagers.[30] In addition, studies with an oral glucose or meal tolerance test each show a higher serum insulin level after two hours and/or a higher insulin area under the curve with a normal glucose response in South Asians compared to different ethnicities.[16;17;19;20;23-25;28;31;32] The response to an insulin tolerance test is also worse in South Asians.[31;32] Moreover, hyperinsulinemic euglycemic clamp studies in men and women of all age groups and with a relatively normal BMI all show lower insulin sensitivity (up to almost 50%) in South Asians compared to different ethnic populations.[16;18;21;23-25;33-36] Thus, South Asians seem to resemble Pima Indians, in whom insulin resistance and hyperinsulinemia are also predominant findings starting from a young age.[37;38]

Insulin secretion or β-cell function has been investigated in fewer studies and with more inferior techniques (e.g. no hyperglycemic clamp studies have been performed) compared to insulin sensitivity in South Asians. In a large study of the UK Prospective Diabetes Study (UKPDS) in 5098 newly diagnosed type 2 diabetes patients (82% white Caucasians, 10% South Asians and 8% Afro-Caribbeans), β-cell function, measured with HOMA %B, was best in South Asians and worse in Afro-Caribbeans, while for insulin sensitivity, measured with HOMA %S, the opposite was true.[15] In another study, in which an intravenous glucose tolerance test (IVGTT) was performed in 17 healthy first degree relatives of patients with type 2 diabetes and 17 healthy controls with no family history of type 2 diabetes, insulin secretory defects prevailed in the European relatives (n=10), whereas insulin resistance was predominant in the South Asian relatives (n=7).[39] Similar results were found in a study in which an oral glucose tolerance test (OGTT) was performed in 260 middle-aged South Asians with different stages of glucose tolerance. They found that impaired glucose tolerance was not associated with a significant defect in insulin secretion, whereas insulin resistance was present already in an early stage of glucose intolerance, suggesting that insulin resistance might precede β-cell deficiency.[40] Another study found that Asian Indian men (n=21) had a ~30% increase in basal β-cell responsivity, measured by the oral C-peptide minimal model, compared to Caucasian men (n=71).[22] Although this increase in β-cell function was inadequate for their degree of insulin resistance as reflected by a lower disposition index, this compensatory increase suggests that β-cell dysfunction is not the main problem. Hence, impairment in insulin secretion does not seem the primary defect in the development of type 2 diabetes in South Asians, in contrast to other ethnicities, such as Japanese and Afro-Caribbeans.[15;41;42]

In the next sections we will describe several possible mechanisms that may contribute to the increased risk of type 2 diabetes, and in particular insulin resistance, in South Asians.

Evolutionary and developmental hypotheses

The excess risk of type 2 diabetes among South Asians has been attributed to several hypotheses (**Table 2**).

The thrifty *genotype* hypothesis states that predisposition to diabetes must have evolved as an adaptive trait in certain environmental situations that later turned disadvantageous due to changes in life style. According to Neel, the thrifty genotype helped survival in the "feast-or-famine days of hunting and gathering cultures", but has now turned detrimental in the modern era of "continuous feasting".[43] In line with the thrifty genotype hypothesis, other evolutionary theories, such as the adipose tissue overflow[44] (see "Body composition and fat distribution"), El Niño[45] and the variable disease selection[46] hypotheses, postulate that South Asians are particularly susceptible to central

Table 2. Evolutionary and developmental hypotheses explaining the excess risk of type 2 diabetes among South Asians.

Hypothesis	Description	Arguments pro/contra
Evolutionary hypotheses		
Thrifty genotype *Neel, 1962*	Predisposition to T2DM must have evolved as an adaptive trait in certain environmental situations that later turned disadvantageous due to changes in lifestyle	Does not explain why South Asians, in particular, are susceptible to central rather than peripheral obesity, or why central obesity is more important than generalized obesity in relation to T2DM.
Adipose tissue compartment *Sniderman, 2007*	The primary adipose tissue compartment is less developed in South Asians due to climatic influences, resulting in early expansion of the secondary adipose tissue compartments, especially in the face of excess energy intake, eventually leading to metabolic disturbances such as dysglycemia and dyslipidemia.	Explains why South Asians are particularly susceptible to central obesity, and why white Caucasians appear to be relatively protected from metabolic abnormalities and diabetes.
El Niño *Wells, 2007*	Susceptibility to central obesity and subsequently to insulin resistance and T2DM is due to nutritional influences. Chronic energy deficiency favours increased allocation to the visceral depot.	Explains why South Asians are particularly susceptible to central obesity. For many generations, South Asians have endured fluctuations of energy supply, associated in turn with global climate patterns (El Niño) and geographic circumstances.
Variable disease selection *Wells, 2009*	Susceptibility to central obesity and subsequently to insulin resistance and T2DM is due to infectious influences. Exposures to varying burdens of infectious disease may have been a selective pressure accounting for genetic ethnic variability in adipose tissue distribution.	Explains why South Asians are particularly susceptible to central obesity. Chronic exposures to endemic gastrointestinal diseases, including cholera, have been a long-term stress in South Asian populations.
Mitochondrial efficiency hypothesis *Bhopal 2009*	Energy producing efficiency of mitochondria enhanced the successful adaptation of South Asians to climatic (heat) and other nutritional exposures (periods of starvation). Instead of using energy to generate heat, South Asian' mitochondria are more likely to produce and subsequently store energy. This mitochondrial efficiency might be disadvantageous when adopting a new lifestyle with low physical activity and a high caloric diet.	Explains the tendency of South Asians to obesity *per se*, central obesity and adverse metabolic outcomes in our current environment, where food is abundant and physical activity is low. Integrates other hypotheses, and offers a biological mechanism (mitochondrial gene mutations).
Developmental hypotheses		
Thrifty phenotype *Hales & Barker, 2001*	An intrauterine disadvantageous environment induces thrifty mechanisms that sets the metabolism to cope with potential future food shortages, which is beneficial for early survival, but increases the risk of T2DM later in life in a nutrient rich environment. Based on strong association between low birth weight and increased risk of T2DM later in life, which is further increased by rapid weight gain in childhood.	Low birth weight and rapid weight gain are common in both native and migrant South Asian neonates. Does not explain why South Asians are susceptible to central rather than peripheral obesity, or why central obesity is more important than generalized obesity in relation to T2DM.

obesity and subsequently to insulin resistance and type 2 diabetes due to selective evolutionary pressures (e.g. climatic, nutritional, or infectious). Recently Bhopal and Rafnsson proposed the mitochondrial efficiency hypothesis: the energy producing efficiency of mitochondria enhanced the successful adaptation of South Asians to climatic (heat) and other nutritional exposures (periods of starvation). Instead of using energy to generate heat, South Asian mitochondria are therefore more likely to produce and subsequently store energy. This mitochondrial efficiency might be disadvantageous when adopting a new lifestyle with low physical activity and a high caloric diet, as is currently the case for South Asians.[47] The study of Nair *et al*. (discussed in "Skeletal muscle"), supports this hypothesis in that they found higher mitochondrial capacity for oxidative phosphorylation in both non-diabetic and diabetic South Asians compared to non-diabetic white Caucasians.[21]

Finally, according to the thrifty *phenotype* hypothesis, a developmental theory, there is a mismatch between intrauterine and adult life environments. An intrauterine disadvantageous environment (due to maternal malnutrition, maternal hyperglycemia, or other maternal/placental influences) induces thrifty mechanisms that sets the metabolism to cope with potential future food shortages, which is beneficial for early survival, but increases the risk of diabetes later in life in a nutrient rich environment.[48;49] This theory is based on the strong association between low birth weight and increased risk of type 2 diabetes later in life observed in a variety of ethnic populations.[50] Low birth weight is common in both native and migrant South Asian neonates.[27;51;52] The risk to develop type 2 diabetes is further increased by rapid weight gain (catch-up growth) in childhood. This applies particularly to countries going through a rapid nutritional transition or when migration takes place from less developed to developed countries, as is the case for both native and migrant South Asians. Interestingly, recent studies in rats showed that intrauterine growth restriction increases the susceptibility to high fat diet induced alterations of fat distribution, adipocyte size, lipid metabolism, and insulin-signalling pathways, supporting the thrifty phenotype hypothesis,[53] and resembling the problem in South Asians.

Although these hypotheses help explain better why South Asians are at an increased risk of developing insulin resistance and type 2 diabetes, they do not give an exact molecular mechanism, except the mitochondrial efficiency hypothesis.

Genetic factors

Type 2 diabetes is considered a polygenic disease that involves polymorphisms of several genes with a high gene-environment interaction.[54] Many loci associated with type 2 diabetes have been found in white Caucasians, however all variants found up till now have a modest effect size, with approximately twofold the lifetime prevalence rate of type 2 diabetes in persons carrying two copies of the risk allele as compared to persons with none.[55]

Most loci found in white Caucasians have been verified in studies with South Asian subjects,[56-58] but few differences between the ethnic groups have been found and the differences are not all consistently shown. For example, Radha *et al*. found that in South Asians the Pro12Ala polymorphism of the peroxisome proliferator activator gamma (PPARγ) gene, which has a protective effect on type 2 diabetes development in white populations, is present at the same frequency in South Asians with and without diabetes and was not associated with a decreased risk of type 2 diabetes.[59] However, in a study in Asian Indian Sikhs they did see a protective effect of the polymorphism, suggesting that there might be differences between specific South Asian groups.[60] An interesting difference might lie in the fat-mass and obesity-associated (FTO) gene, which holds the strongest known obesity-susceptibility locus in Europeans. An association with type 2 diabetes has also been shown, but this seemed to be secondary to obesity. In South Asians however, the FTO polymorphism was found to be associated with type 2 diabetes independently of BMI,[61-63] implying that in South Asians there may be a different relationship between BMI and type 2 diabetes. However, associations between FTO and type 2 diabetes that were mediated by obesity have been found in South Asians as well[64] and in a study in North India none of the FTO variants was even associated with type 2 diabetes.[65] Two other recent studies in South Asians found polymorphisms of genes related to skeletal muscle; one associated with abdominal obesity and low lean body mass (*myostatin*)[66], and one contributing to type 2 diabetes susceptibility (*SCGC*)[67], which merit further investigation.

Thus, so far no clear genetic differences between white Caucasians and South Asians have been found. Interestingly, most loci associated with type 2 diabetes are related to impaired β-cell function and insulin secretion, which is not considered the primary defect in the South Asian population, as discussed before. Therefore, differences between the two ethnic groups on these loci is unlikely. However, an exceptionally high percentage of South Asians have a positive family history of type 2 diabetes, making it likely that genetic differences are somehow involved in the increased prevalence of TDM and insulin resistance in this ethnic group.

Diet and exercise

An unhealthy diet is a known risk factor for type 2 diabetes. Various studies have reported a number of dietary imbalances in South Asian diets associated with insulin resistance, such as high intake of total fat, saturated fatty acids, long chain ω-6 polyunsaturated fatty acids (PUFA), *trans*fatty acids, and carbohydrates, and low intake of monounsaturated fatty acids, long chain ω-3 PUFAs, fibre and several micronutrients (e.g. magnesium, calcium, vitamin D).[68-73] Furthermore, children and adolescents already have a high intake of ω-6 PUFA and a low intake of ω-3 PUFA, which is correlated with fasting hyperinsulinemia.[74;75] However, supplementation of ω-3 PUFAs (fish oil) did not improve insulin sensitivity in South Asians.[69;76] Moreover, other studies even reported that South Asian diets are healthier compared to Caucasian diets (lower intake of fat).[73;77-79] Furthermore, different regional and religious South Asian communities in the United Kingdom (UK) all had a similar, markedly higher prevalence of diabetes compared to white Europeans, despite the known dietary, cultural and socioeconomic differences between these different South Asian communities. In addition, there were no discernible differences in the dietary customs of those with normal glucose tolerance, impaired glucose tolerance and newly diagnosed type 2 diabetes.[80;81] Lack of exercise is another risk factor for type 2 diabetes. The 2004 Health Survey for England data reported lower levels of physical activity in South Asian groups compared to the general UK population and other ethnic minority groups,[77] and other studies showed similar results in migrant and urban South Asians.[6;15;82-87] This low level of physical activity is already present in children and adolescents.[77;85;88-91]

Hence, although lifestyle factors will certainly play a role in the etiology of insulin resistance as they do in white Caucasians, there is no reason to assume that this role is any different between both ethnicities. This is strengthened by the fact that the excessive risk for type 2 diabetes applies to both native and migrant South Asians despite differences in lifestyle. Hence, South Asians seem to have an exceptionally high susceptibility to develop type 2 diabetes in the context of the same environmental pressure when compared to other ethnicities.

Body composition and fat distribution

South Asians develop insulin resistance and type 2 diabetes at lower ranges of BMI than white Caucasians. An equivalent incidence rate of type 2 diabetes is seen at a BMI of 24 kg/m^2 in South Asians compared to 30 kg/m^2 in Caucasian subjects.[92] Gray *et al*. even showed an equivalent level of dysglycemia at a BMI cut-off point of 22.6 kg/m^2 in South Asian males as compared to 30.0 kg/m^2 in white Caucasian males.[93] In addition, a cross-sectional study of 4633 9- to 10-year-old children of South Asian, black African-Caribbean and white European origin showed that South Asian children were more metabolically sensitive to adiposity as indicated by stronger positive associations between HOMA-IR and adiposity measures.[94] It has been proposed that an increase in total fat mass and an adverse pattern of fat distribution contributes to the higher risk of type 2 diabetes in South Asians at similar BMI levels. Therefore, it has been suggested that ethnic-specific BMI cut off values should be used for assessing diabetes risk in different populations.

Several studies have shown that South Asians have a higher percentage of body fat for comparable levels of BMI compared with white Caucasians and are therefore referred to as 'metabolically obese' (**Table 3**).[16;23;34;95-97] This is already apparent in children and

Table 3. Differences in body composition in South Asians *vs.* white Caucasians

South Asians *vs.* **white Caucasians**	*References*
Higher percentage of body fat	16;23;34;95-97
Thin fat phenotype in neonates	27;101-103
Increased abdominal adiposity	16;23;34;95;96
Increased VAT	23;96
Increased deep SAT, lower or similar superficial SAT	109;110
Decreased skeletal muscle mass/lean body mass	16;95;109;146

VAT: visceral adipose tissue; SAT: subcutaneous adipose tissue.

adolescents.[98-100] Also the distribution of fat differs between ethnicities. South Asian neonates exhibit the 'thin-fat phenotype', described as low muscle mass with preserved subscapular (central) fat[27;101;102] and this phenotype is retained in Surinam South Asian babies of the fourth to fifth generation after migration from India.[103] Modi *et al*. showed that South Asian neonates have significantly increased abdominal adiposity as compared to European babies[104] and this increase in abdominal adiposity has also been observed in adults in several other studies.[16;23;34;95;96] The 'thin-fat phenotype' is also apparent in pre-pubertal Indian children who have greater adiposity than white UK children despite significantly lower BMIs.[29]

It is currently unclear which of the abdominal adipose tissue compartments, visceral adipose tissue (VAT) or subcutaneous adipose tissue (SAT), has the most detrimental effect on insulin sensitivity.[44] Banerji *et al*. showed that South Asians have high amounts of VAT and that insulin resistance is correlated with total visceral and not subcutaneous abdominal adipose tissue volume.[16] Other studies also showed an association of VAT with diabetes[105] and cardiovascular risk factors in South Asians.[106;107] However, in a study of Raji *et al*., insulin sensitivity measured with a hyperinsulinemic euglycemic clamp in healthy South Asians and white Caucasians was inversely related with VAT as well as abdominal SAT and total abdominal adipose tissue.[23] This was however a small study including only 12 South Asian and 12 white Caucasian subjects. In another study in 171 South Asians, abdominal SAT was a better predictor of the metabolic syndrome. Also, SAT (and not VAT) was significantly correlated with insulin resistance, however insulin resistance was measured by HOMA and data were available for 46 patients only.[108] Furthermore, Chandalia *et al*. showed that insulin resistance was present in South Asians who had higher percentages of total body fat and abdominal SAT, but similar amounts of VAT as compared to white Caucasians.[34] However, these studies do not discriminate between superficial SAT (SSAT) and deep SAT (DSAT). It is believed that an increase in DSAT, similar to VAT, is associated with metabolic disturbances.[44] Sniderman *et al*. theorized in their 'overflow hypothesis' that SSAT is the primary adipose tissue compartment and DSAT and VAT are secondary compartments, which have adverse metabolic consequences.

They propose that South Asians have a less developed primary compartment, resulting in earlier expansion of the secondary compartment, thereby leading to the increased risk of type 2 diabetes and cardiovascular disease.[44] Studies showing that South Asians have higher levels of DSAT and lower or similar amounts of abdominal SSAT as compared to white Caucasians support this hypothesis.[109;110]

Thus, South Asians have higher total fat mass than white Caucasians. This fat is primarily stored in the visceral and deep subcutaneous compartments and correlates with insulin resistance. This might be due to different metabolic characteristics of adipocytes in this compartment as discussed below.

Adipose tissue dysfunction and inflammation

Not only the amount and distribution of body fat differs between South Asians and white Caucasians. It has been proposed that South Asians have abnormalities in adipocyte function as well (**Table 4**). Adipocytes serve as buffer for the daily influx of fat. When adipocytes are overloaded, for example in case of obesity, they become dysfunctional; the ability to store lipids is decreased.[111] Studies have shown that South Asians have significantly increased subcutaneous adipocyte size.[34;109] Hypertrophic adipocytes are thought of as dysfunctional and appear to be associated with insulin resistance in non-diabetic individuals independent of BMI and to be an independent predictor for the development of type 2 diabetes.[112;113] Furthermore, Balakrishnan *et al*. showed that South Asians not only have a higher fraction of very large adipocytes, but also exhibit a higher ratio of small-to-larger adipocytes, which is considered a defect in adipose tissue maturation, resulting in a decreased storage capacity of triglycerides.[114] Also, in a recent study, normoglycemic young South Asian men were shown to have increased expression of *col6a3* in SAT, which is known to reduce adipocyte maturation.[36]

Table 4. Differences in adipose tissue in South Asians *vs.* white Caucasians

South Asians *vs.* **white Caucasians**	*References*
Increased adipocyte size	34;109;114
Increased FFA release	115
Increased leptin	18;22;115;117-119
Decreased adiponectin	36;119;124;125
Increased IL-6 and TNF-alpha release	22;131
Increased CRP production	132;133

Adipocyte dysfunction was also shown in a study of Abate *et al*., demonstrating that non-diabetic South Asians have higher fasting levels of free fatty acids (FFAs) compared to white Caucasians, even when adjusted for body fat content, and fail to completely suppress plasma FFA concentration during hyperinsulinemia induced by an OGTT.[115]

This suggests that in healthy South Asians insulin is unable to sufficiently inhibit lipolysis, resulting in an excess efflux of FFA, which may play a role in the development of type 2 diabetes.

White adipose tissue not only has a function in the storage and release of FFAs, but is more and more recognized as an endocrine organ secreting several proteins called adipocytokines. Of those, leptin and adiponectin are the most frequently studied in relation to insulin resistance and type 2 diabetes. Leptin has an important role in food intake, energy expenditure and glucose metabolism. Leptin seems to have a glucose- and insulin-lowering and insulin-sensitising effect on the whole body level. Plasma leptin levels are positively correlated with plasma insulin, BMI and body fat content, therefore obesity reflects a state of leptin-resistance.[116] Plasma leptin levels were increased in South Asians as compared to Caucasian subjects in several studies[18;22;115;117-119] independent of overall or abdominal obesity. Leptin levels were found to be correlated with SAT and not with VAT.[16;120] However, in some of these studies a difference in fat mass was present between the two groups, or data on fat mass were not reported. Furthermore, in a recent study, no correlation was shown between leptin and insulin resistance in South Asians.[121]

In contrast to leptin, adiponectin is decreased in obesity, insulin resistance and type 2 diabetes.[122] Adiponectin is thought to exert insulin-sensitizing, antiatherogenic and anti-inflammatory effects.[123] South Asians exhibit lower levels of adiponectin compared to white Caucasians.[36;119;124] This is already apparent in babies of 3-6 months old.[125] Furthermore, lower adiponectin levels have been found in South Asians with impaired glucose tolerance and type 2 diabetes as compared to normal glucose tolerant South Asian individuals.[121;126] In addition, low adiponectin levels were found to be an independent predictor for type 2 diabetes development in South Asians.[127] However, another study showed no relation between adiponectin and insulin sensitivity in the South Asian group.[128]

Dysfunctional adipose tissue also produces pro-inflammatory cytokines, such as TNF-α and IL-6, leading to a chronic inflammatory state. Although not yet fully elucidated, it is hypothesized that activation of proinflammatory pathways in for example muscle, liver, and adipose tissue, leads to insulin resistance by inhibiting the insulin signalling cascade.[129;130] Middle-aged South Asian women were shown to exhibit significantly higher IL-6 levels than Europeans, however no ethnic difference in IL-6 was detected among men.[131] In young South Asian men however, Il-6 levels were found to be elevated as compared to white Caucasians.[22] In this study, TNF-α was elevated as well, yet this difference disappeared when correcting for insulin sensitivity. In addition, in comparison to white Caucasians, studies showed higher C-reactive protein (CRP) levels in South Asians, also suggesting a state of low grade inflammation.[132;133] The primary production site of CRP is the liver, and not adipose tissue. However, visceral fat is drained by the portal vein to the liver and CRP production is induced by cytokines, such as IL-6.[129] In South Asians, visceral fat was positively associated with CRP levels, independent of total adiposity and was associated with fasting and 2-h insulin levels during an OGTT.[133]

In conclusion, dysfunctional adipose tissue and inflammation are likely to contribute to the South Asian phenotype of increased insulin resistance and type 2 diabetes. It is, however, difficult to determine the primary defect: adipocyte dysfunction leads to abnormalities in the insulin signalling pathway, or vice versa: abnormal insulin signalling results in adipocyte dysfunction. Abate *et al*.[115] proposed that it might be a vicious cycle starting with primary insulin resistance, leading to adipose tissue dysfunction, which is reflected by the increased secretion of FFAs and (adipo)cytokines. The high levels of circulating FFAs in turn can aggravate insulin resistance through the deposition of triglycerides in non-adipose tissues,[134] also called ectopic fat.

Ectopic fat

Insulin resistance and type 2 diabetes are associated with ectopic fat accumulation, i.e. the storage of triglycerides in nonadipose tissues such as the liver, heart, and skeletal muscle. Intracellular lipid deposition in these tissues is a consequence of oversupply of FFAs due to increased caloric intake, obesity, adipocyte dysfunction, increase in fatty acid transporters and/or impairment in mitochondrial lipid oxidation. The subsequent accumulation of intermediates of lipid metabolism, such as long-chain acyl-CoA, diacylglycerol, and ceramids, in these organs appears to disrupt normal metabolic processes, causing organ-specific dysfunction.[134]

Deposition of fat in the liver in the absence of excessive alcohol intake is referred to as nonalcoholic fatty liver disease (NAFLD), and is associated with hepatic insulin resistance.[135;136] This is due to a reduction in insulin-stimulated hepatic glucose uptake and decreased insulin suppressibility of hepatic glucose production, which both contribute to increased plasma glucose levels.[134] In South Asians, limited data have reported higher hepatic triglyceride content in comparison to white Caucasians, as measured by ^{1}H-MRS.[22;109] Petersen *et al*. showed that young healthy South Asian men (n=23) had a higher prevalence of insulin resistance, as assessed with an OGTT in combination with the insulin sensitivity index, which was associated with a ~2-fold increase in hepatic triglyceride content compared with Caucasian men (n=73).[22] Another study reported higher fat infiltration in the liver in adult South Asians (n=56) *vs.* white Caucasians (n=52).[109] These data suggest that South Asians appear to be predisposed to develop hepatic steatosis, associated with hepatic insulin resistance.

In non-athletic white Caucasians, intramyocellular lipid (IMCL) accumulation is associated with insulin resistance and type 2 diabetes, due to its toxic effects on insulin signalling.[137-139] In South Asians, IMCL content seems to be higher compared to white Caucasians.[22;140] However, in contrast to white Caucasians, no correlation between IMCL and insulin resistance has been found in South Asians so far.[22;109;140-143] This suggests that IMCL is of less significance to skeletal muscle insulin sensitivity in South Asians as compared to Caucasians.

Role of skeletal muscle

Muscle glucose uptake accounts for 75-80% of whole-body insulin-stimulated glucose disposal.[144] Total body muscle mass (relative to body size) has been shown to exert an independent effect on insulin sensitivity and glucose disposal.[145] Several studies reported that skeletal muscle mass, or lean body mass, is lower in South Asians than in white Caucasians.[16;95;97;100;109;146] Furthermore, low muscle mass was associated with reduced insulin sensitivity in young, lean South Asian men.[147] In studies conducted at our research centre, we also found lower lean body mass in healthy young South Asian men compared to BMI-matched Caucasians, as measured by dual-energy x-ray absorptiometry (DEXA) scan (unpublished data).

In Caucasian type 2 diabetes patients the primary defect at the skeletal muscle level seems to reside in non-oxidative glucose disposal (NOGD), i.e. glycogen synthesis, due to impairments in insulin-stimulated GLUT-4 translocation leading to impaired glucose transport.[148-150] These impairments in the insulin signalling pathway seem to be induced by defects in mitochondrial fatty acid oxidation and/or increased delivery of fatty acids, leading to IMCL. IMCL, in turn, can impair insulin signal transduction.[134] Indeed, in type 2 diabetes patients a number of defects in the insulin signalling pathway have been found.[151] Furthermore, reduced mitochondrial density with reduced oxidative phosphorylation have been described in insulin-resistant offspring of patients with type 2 diabetes.[152] Moreover, maximal oxygen uptake, or VO_{2max} (a measure of whole-body oxidative capacity), is found to be a strong independent predictor of peripheral insulin sensitivity in white Caucasians,[153-155] and low cardiorespiratory fitness is associated with low skeletal muscle lipid oxidative capacity.[156] One might speculate, therefore, that the increased risk of insulin resistance and type 2 diabetes in South Asians might be, at least in part, explained by reduced skeletal muscle oxidative capacity.

In South Asians, several studies reported lower VO_{2max} values in South Asians compared to matched white Caucasians.[89;146;157] A recent study of Ghouri *et al.* confirmed this finding in middle-aged South Asian men without type 2 diabetes (n=87) compared to age- and BMI-matched European men (n=99) and, importantly, found that the lower cardiorespiratory fitness explained 68% of the ethnic difference in HOMA-IR.[97] Of note, the lower VO_{2max} could not be explained by their lower levels of physical activity, indicating that low physical fitness is an innate feature of the South Asian phenotype. However, so far only two relatively small in-depth studies have been performed in South Asians, in which skeletal muscle biopsies were obtained to find out more about the molecular mechanisms of the increased risk of insulin resistance and type 2 diabetes in this ethnicity. In a study of Nair *et al.* no impairment in mitochondrial function (measured as skeletal muscle mitochondrial capacity for oxidative phosphorylation (OXPHOS) as assessed by mitochondrial DNA copy number (mtDNA), OXPHOS gene transcripts, citrate synthase activity, and maximal mitochondrial ATP production rate (MAPR)) was found in 13 healthy, middle-aged South Asians living in the USA, even despite the finding that they were more insulin resistant than 13 age-, sex- and BMI-matched Northern European Americans. On the contrary: South Asians had even higher mitochondrial capacity for oxidative phosphorylation.[21] Hall *et al.* also reported that healthy, young, lean male South Asians (n=20) compared to age- and BMI-matched white Caucasians (n=20) did not exhibit lower expression of skeletal muscle oxidative and lipid metabolism genes, and mitochondrial DNA to nuclear DNA ratio (index of mitochondrial biogenesis) did not differ between groups. Gene expression of carnitine palmitoyltransferase 1A (CPT1A) and fatty acid synthase (FASN), both involved in lipid metabolism, was even higher in South Asians.[146] Consequently, both studies concluded that mitochondrial dysfunction did not account for the observed insulin resistance in South Asians. Importantly, Hall also showed that South Asians oxidized less fat during submaximal exercise, whereas the resting rate of fat oxidation did not differ between groups. This difference, however, was not reflected in reduced skeletal muscle expression of oxidative and lipid metabolism genes.[146] It should be noted, however, that these results are derived from only two relatively small studies in different age groups, and thus extrapolation of these results to the whole South Asian population should be done with caution.

The above-mentioned study of Hall *et al.* is the only study that compared skeletal muscle insulin signalling between both ethnicities.[146] Interestingly, this study showed that South Asians had reduced skeletal muscle protein expression of key insulin signalling proteins (phosphatidylinositol 3'-kinase p85 subunit (PI3K (p85)) and protein kinase B serine 473 phosphorylation (pPKB-Ser473)). Basal Ser473 phosphorylation of PKB was even 60% lower in South Asians, and was significantly correlated with whole-body insulin sensitivity. However, the expression of the insulin signalling proteins in hyperinsulinemic condition was assessed in response to maximal insulin stimulation via incubation for 10 minutes in the presence of 10 nM human soluble insulin, instead of using a hyperinsulinemic clamp. Hence, the meaning of this finding needs to be corroborated.

To summarize, South Asians have less skeletal muscle mass and seem to have lower cardiorespiratory fitness and reduced capacity for fat oxidation during submaximal exercise, all correlating with their reduced whole-body insulin sensitivity, which is not reflected in reduced expression of oxidative and lipid metabolism genes in skeletal muscle.[146] However, so far only two relatively small in-depth studies have been performed in South Asians, therefore these results should be interpreted with caution and more research is warranted.

Nitric oxide bioavailability: endothelial and HDL-cholesterol dysfunction

Apart from the aforementioned metabolic functions, insulin also stimulates the release of nitric oxide (NO) from endothelium, which leads to peripheral vasodilatation, increased capillary recruitment and increased blood flow. Subsequently, these hemodynamic actions increase the delivery of insulin to (underperfused) tissues and enhance the delivery of glucose and other substrates to skeletal muscle. It is thought that 25-40% of insulin-mediated glucose disposal is due to its hemodynamic effects.[158;159]

Several studies have demonstrated that South Asians have lower NO bioavailability compared to white Caucasians.[160;161] NO is mainly produced by the endothelium as a consequence of an interaction with high density lipoprotein (HDL)-cholesterol.[162;163] Thus, a diminished NO bioavailability might be caused by dysfunction of the endothelium and/or dysfunctional HDL. To what extent lower NO availability is present in South Asians as well as its cause, endothelial or HDL dysfunction or a combination of both, are yet unknown.

Endothelial dysfunction is defined as inadequate endothelial-mediated vasodilatation and is present in patients with obesity, dyslipidemia, diabetes and very early in individuals with (a high risk of) atherosclerosis. Insulin resistance and endothelial dysfunction are closely related. It has been shown that gluco- and lipotoxicity decrease NO availability.[158;159] In South Asians impairments in endothelial function have been demonstrated. Chambers *et al*. showed that endothelium-dependent dilatation (measured as brachial artery flow mediated dilatation) was reduced in South Asians living in the UK as compared to white Caucasians and this was confirmed by others.[161;164] In yet another study, although no difference in vasodilatation was observed after reactive hyperemia or sublingual nitroglycerin administration between the two ethnic groups, the increase in vasodilatation during hyperinsulinemia as compared to basal conditions was significantly lower in South Asians.[24] Signs of endothelial dysfunctions are already present early in life in South Asians. Din *et al*. showed that healthy, young South Asian men have increased arterial stiffness (reflected by an increased augmentation of radial artery pressure waveforms) compared to matched white Caucasians.[165] Interestingly, in cord blood of South Asian neonates an elevated level of E-selectin, a marker of endothelial dysfunction which has been shown to predict the occurrence of type 2 diabetes in adult women, was found, suggesting that endothelial dysfunction might already be present at birth.[26] Furthermore, it was shown that South Asians have lower circulating numbers of endothelial progenitor cells (EPCs) and EPC colony forming units, which may result in a reduced capacity for endothelial repair.[160;161] However, others did not find a difference in the EPC count between South Asian and Caucasian men with established atherosclerosis.[166]

Besides endothelial dysfunction, HDL dysfunction might also play a role in the decreased NO bioavailability observed in South Asians. Multiple studies have consistently shown lower HDL-cholesterol levels in South Asians compared to white Caucasians.[19;20;23;33;99;132;167] Not only do they have lower levels of HDL-cholesterol, they also seem to have more small-dense dysfunctional HDL particles, which are thought to be proinflammatory and less protective compared to normal HDL particles..[168]

A diminished NO bioavailability in South Asians might thus be caused by both endothelial and HDL dysfunction, and might be a factor in the increased incidence of type 2 diabetes and cardiovascular disease in this ethnic group.

CONCLUSION & FUTURE DIRECTIONS

The risk of developing type 2 diabetes is exceptionally high among both native and migrant South Asians, comprising one fifth of the worlds' population. The disease develops about a decade earlier than in white Caucasians and South Asians also have an increased incidence of retinopathy, nephropathy and coronary artery and cerebrovascular disease. Even non-diabetic individuals have higher insulin levels compared to other ethnic groups regardless of age, gender or BMI. This points to an impairment in insulin sensitivity. Indeed, several studies have shown that the predominant mechanism leading to the increased risk of type 2 diabetes in South Asians seems to be insulin resistance rather than decreased β-cell function.

We have tried to review several pathogenetic factors that might underlie the increased and accelerated risk to develop insulin resistance and type 2 diabetes in South Asians, which is illustrated in **Figure 2**.

Given the strong familial clustering of type 2 diabetes in South Asians, one would assume distinctive genetic differences between white Caucasians and South Asians. However, the presence of polymorphisms associated with type 2 diabetes found thus far do not clearly differ between the two ethnicities. It might be that either the wrong loci have been investigated (i.e. South Asians have different polymorphisms), the sample sizes were too small, or that the increased risk is caused by epigenetic differences. We believe that genetics or epigenetics must play a role, despite the fact that this has not been confirmed yet.

South Asians unmistakably have a different body composition than white Caucasians with relatively thin extremities and increased abdominal adiposity, both in the visceral as well as in the deep subcutaneous compartments. Increased visceral and deep subcutaneous fat mass are associated with insulin resistance. Up till now, however, studies in South Asians show contradictory results with either an association of VAT with insulin resistance or of SAT with insulin resistance. Furthermore, South Asians appear to have dysfunctional adipocytes, leading to a decreased storage capacity for triglycerides

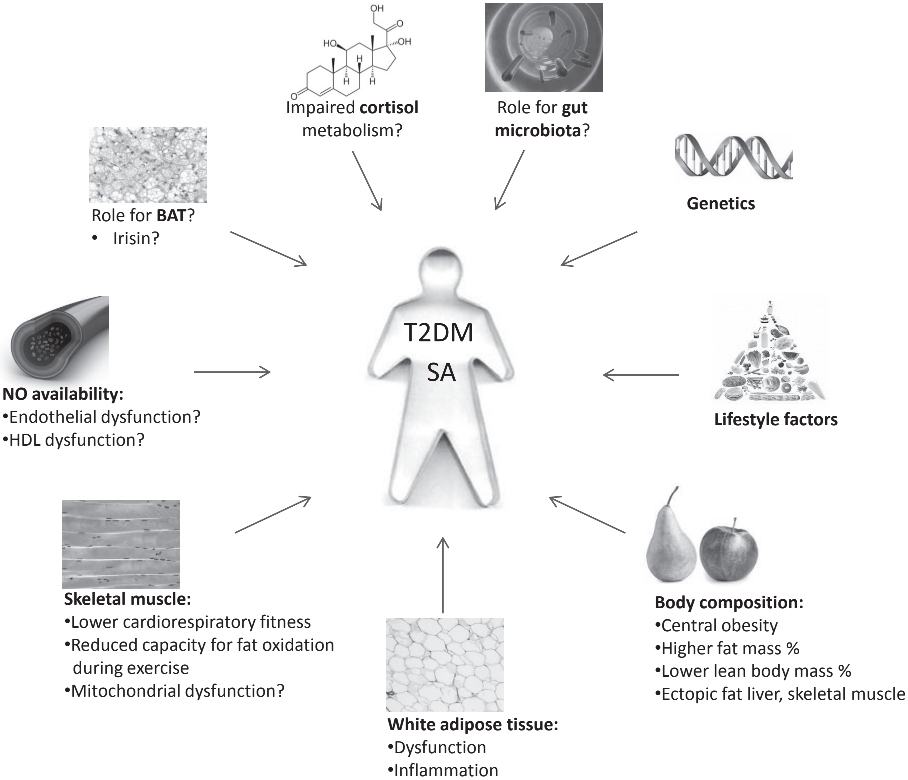

Figure 2. Potential pathophysiological mechanisms that may underlie or contribute to the increased risk of type 2 diabetes in South Asians as compared to white Caucasians.

and impaired release of FFA's, adipokines and pro-inflammatory cytokines, which are thought to disrupt the insulin signalling pathway.

Remarkably, as of yet no convincing differences in intracellular signalling cascades and enzymatic process involved in insulin signalling have been found between South Asians and Caucasians. However, so far only two relatively small studies obtained muscle biopsies and investigated mitochondrial function, and only one investigated the insulin signalling pathway. Some studies show differences in endothelial function, suggesting that perhaps impaired insulin-mediated capillary recruitment plays a role in the development of insulin resistance in South Asians. This would lead to diminished delivery of insulin to its site of action. Hence, perhaps the fact that no difference in insulin signalling was observed is a quantitative problem.

Differences in dietary habits do not seem to play an important role in the increased diabetes risk. The number of studies examining the effect of exercise are small but consistently show – self-reported – lower daily activity levels and lower cardiorespiratory fitness (maximal oxygen uptake $VO2_{max}$) in South Asians, which appears to contribute to the increased level of insulin resistance. Further research should not only focus on duration and intensity of physical activity and exercise (endurance *vs.* strength) but also on the underlying cellular mechanisms.

We think there are several other areas of interest that should be explored in South Asians to further investigate the increased risk for insulin resistance and type 2 diabetes. Firstly, brown adipose tissue. Brown adipose tissue burns triglycerides and glucose to generate heat through a process called mitochondrial uncoupling[169]. Since brown adipose tissue is involved in around 20% of total energy expenditure[170] and clearance of serum triglycerides and glucose, it could play a role in the disturbed metabolic phenotype of South Asians. Secondly, and in light with the interest in brown adipose tissue, is Irisin. Irisin is a recently discovered myokine that increases with exercise and is, at least in rodents, involved in browning of white adipose tissue.[171] Given the fact that South Asians have lower muscle mass and lower physical activity levels the role of Irisin in insulin resistance and amount of brown adipose tissue should be further explored. Thirdly, the gut microbiota of South Asians might be quite different from white Caucasians. The gut microbiota of obese subjects appears to be different from that of lean subjects and is thought to be associated with insulin resistance.[172] Fourthly, the thin-fat phenotype might suggest differences in the hypothalamic-pituitary-adrenal axis with (tissue-specific) impaired cortisol metabolism.

As for now, we conclude that the strong genetic predisposition for type 2 diabetes in South Asians should be explained by as of yet undiscovered polymorphisms that negatively interact with environmental factors such as Western-type diet and low physical activity level. In addition, genetic makeup accounts for the disadvantageous body composition with low muscle mass and increased visceral fat mass. The ensuing effects on release of pro-inflammatory adipocytokines, myokines and FFAs disrupt cellular processes and induce insulin resistance.

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