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Title

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Permalink

<https://escholarship.org/uc/item/3hv514bp>

Journal

Current Cardiology Reports, 16(5)

ISSN

1523-3782

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Publication Date

2014-05-01

DOI

10.1007/s11886-014-0476-5

Peer reviewed



Published in final edited form as:

Curr Cardiol Rep. 2014 May ; 16(5): 476. doi:10.1007/s11886-014-0476-5.

Diabetes and Associated Complications in the South Asian Population

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Abstract

The increasing prevalence of diabetes in South Asians has significant health and economic implications. South Asians are predisposed to the development of diabetes due to biologic and lifestyle factors. Furthermore, they experience significant morbidity and mortality from complications of diabetes, most notably coronary artery disease, cerebrovascular disease and chronic kidney disease. Therefore, understanding the pathophysiology and genetics of diabetes risk factors and its associated complications in South Asians is paramount to curbing the diabetes epidemic. With this understanding, the appropriate screening, preventative and therapeutic strategies can be implemented and further developed. In this review, we discuss in detail the biologic and lifestyle factors that predispose South Asians to diabetes and review the epidemiology and pathophysiology of microvascular and macrovascular complications of diabetes in South Asians. We also review the ongoing and completed diabetes prevention and management studies in South Asians.

Keywords

South Asians; type 2 diabetes; diabetes risk factors; diabetes complications; genetics of diabetes; diabetes prevention

Introduction

The prevalence of diabetes worldwide is predicted to increase by 69% in adults in developing countries between 2010 and 2030.¹ Between 2010 and 2030, diabetes prevalence is expected to increase by 72% in India, from 7.6% to 9.1%, with an estimated 87 million diabetic adults by year 2030¹. Data from the U.S. National Health Interview Survey from 1997–2008 showed that age- and sex-adjusted prevalence of type 2 diabetes in the U.S. was higher in Asian Americans (4.3–8.2%) than in whites (3.8–6.0%) and most notably, Asian Indians had the highest odds of diabetes². A population-based study of U.S.

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Conflict of Interest

Arti Shah and Alka M. Kanaya declare that they have no conflict of interest.

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Asian Indians found diabetes prevalence in adults was 17% compared to 8% in non-Hispanic whites, 13% in non-Hispanic blacks, 10% in Hispanic Latinos and 15% in Native Americans/Alaskan natives³. Dampening the spread of diabetes across the South Asian population has significant health and economic implications.

This increasing prevalence of diabetes in South Asians is multifactorial – due to both biologic and lifestyle factors, with urbanization and immigration playing a large role. South Asians have increased visceral adiposity and insulin resistance, impaired β -cell function, and a genetic predisposition to diabetes which culminates in a markedly increased risk of diabetes.^{4–6} Additionally, urbanization across Asia is leading to decreased physical activity, increased intake of dietary fats and processed foods and increased mental stress which amplify the effects of insulin resistance and abdominal obesity.^{4,6} Migration to more affluent countries has further contributed to the increasing prevalence of diabetes.⁶

The health burden of diabetes and associated mortality is largely due to its microvascular and macrovascular complications – particularly cardiovascular disease. South Asians newly diagnosed with type 2 diabetes have a higher prevalence of complications at the time of diagnosis compared to Europeans – macrovascular disease (15.7% vs. 9.4%) and microvascular disease (27.3% vs. 16.5%) including retinopathy and nephropathy.⁷ Several studies have demonstrated that compared to other ethnic groups, South Asians with diabetes have a higher mortality rate.^{8,9}

The increasing prevalence of diabetes among South Asians along with the higher complication and mortality rate in this population urge the need for further research investigating the risk factors that predispose South Asians to diabetes and culturally tailored interventions that delay or prevent diabetes development. There is an urgent need for healthcare providers to identify and treat modifiable risk factors and for health organizations to develop and sustain programs that focus on diabetes prevention in South Asians. In this review, we discuss in detail the risk factors that predispose South Asians to diabetes, the macrovascular and microvascular complications among South Asians and preventative strategies that aim to curb this epidemic.

Factors that Predispose South Asians to Diabetes

Biologic Factors

Insulin Resistance—South Asians have a higher degree of insulin resistance (IR) compared to other ethnic groups and which plays a vital role in the development of diabetes. In the 1980s, Mohan et al. evaluated differences in the insulin response to an oral glucose load in Asian Indians compared to Europeans.¹⁰ In both non-diabetic and diabetic Asian Indians, basal insulin levels were higher and insulin response to a glucose load was also higher suggesting that Asian Indians need higher levels of insulin to maintain euglycemia and secrete insulin at higher rates in response to same amount of glucose.¹⁰

This increased IR in South Asians is partly explained by fetal adaptations that have become detrimental during modern day. The “thrifty genotype” hypothesis proposes that individuals can efficiently store energy during times of food abundance giving them a survival

advantage during times of famine. With urbanization and immigration, this genotype now predisposes individuals to IR and diabetes.¹¹ The alternative explanation is the “thrifty phenotype” hypothesis which proposes that poor intrauterine nutrition leads to fetal adaptations in preparation for a life of starvation which leads to IR as these adaptations persist into childhood and adulthood.¹¹ Bavdekar et al.¹² demonstrated in 8 year old Indian children that lower birth weight was associated with increased IR as measured by homeostasis model assessment (HOMA). In a healthy adolescent urban South Indian population, IR was found in 30–55% of adolescents¹³. IR is associated with cardiometabolic risk factors, including elevated triglycerides, elevated fasting plasma glucose and elevated blood pressure and with body composition parameters, including BMI, waist circumference and body fat percentage.¹³

This predisposition to IR persists into adulthood. Scholfield et al demonstrated Asian Indian vegetarians had significantly higher insulin levels compared to American vegetarians both in the fasting state and after an oral glucose load and a higher insulinogenic index.¹⁴ Despite having comparable diets, Asian Indians were more likely to be insulin resistant. Also, Asian Indian men tend to be more insulin resistant than Caucasian men independent of truncal and generalized adiposity implying a metabolic defect.¹⁵ And a multi-ethnic study of healthy, young, lean adults demonstrated that Asian Indians, especially men, had a 2–3 fold higher prevalence of IR compared to other ethnic groups.¹⁶

Pancreatic β -cell Dysfunction—Further increasing the risk of diabetes in South Asians is β -cell dysfunction. Once there is hyperglycemia, β -cell dysfunction is evident in those with type 2 diabetes.¹⁷ However, β -cell dysfunction precedes the development of hyperglycemia and diabetes in South Asians. Petersen et al evaluated β -cell responsiveness to an oral glucose load in healthy, lean Asian Indian and Caucasian men.¹⁶ Asian Indians had a 28% higher basal β -cell responsiveness compared with Caucasian men, but it was inadequate for their degree of IR as reflected by 60% lower disposition index.¹⁶ In Indians living in South Africa, those with impaired glucose tolerance had delayed insulin responses after an oral glucose load¹⁸ suggesting early β -cell dysfunction. A recent study done in Asian Indians in Chennai, India demonstrated that the oral disposition index, a marker of β -cell function, was more closely associated with dysglycemia than HOMA-IR.¹⁹

Body Composition—For a given BMI, South Asians have a higher amount of total body fat compared to Caucasians²⁰ and higher amounts of abdominal adipose tissue including both subcutaneous fat and visceral fat.^{15,21} Adipose tissue is an active endocrine organ and intra-abdominal adipose tissue is strongly linked to IR in South Asians.²² The increased risk of diabetes in South Asians is partly explained by body composition.

This predisposition to adiposity and IR begins during fetal development in South Asians. Yajnik et al found that Indian babies were lighter and had smaller anthropometric measurements compared to babies born in the U.K., however the skinfold thickness was the most preserved measurement.²³ This demonstrated that Indian babies preserved body fat during their intrauterine development which predisposes to future IR. Similar results were found in a study of South Indian children²⁴ in which subscapular skinfold thickness was larger in the Indian children while the other body measurements was smaller. Predictors of

neonatal subscapular thickness included maternal BMI, maternal nutrition and socioeconomic status.^{23,24} This finding led to the concept of the thin-fat Indian baby where these babies are actually thin by weight but have relatively more adipose tissue. This higher subscapular thickness indicates a propensity for central body fat preservation^{23,24} which is associated with IR. This concept supports the “thrifty phenotype” hypothesis discussed above. Bhargava et al followed a cohort born in Delhi who had a 10.8% impaired glucose tolerance and 4.4% diabetes prevalence as young adults. These adults had low BMI up to the age of two years followed by an early adiposity rebound and an accelerated increase in BMI until adulthood, with average BMI 26.2 kg/m².²⁵ Thinness in infancy was associated with abnormalities in glucose metabolism in adulthood.

Several studies in South Asian adults have investigated the role of body composition, especially abdominal obesity, in the development of IR and metabolic abnormalities. McKeigue et al found that glucose intolerance was more strongly associated with waist-hip ratio (WHR) than with BMI and skinfold measures in a South Asian and European population.²⁶ For a given BMI, compared to Caucasians, Asian Indians have high levels of generalized obesity, including increased total body fat, subcutaneous fat and visceral fat, which are not always reflected in their non-obese BMI^{27–30}. This increased visceral fat has been associated with increased IR, dyslipidemia and metabolic syndrome which increase the risk for diabetes and cardiovascular disease.^{27–30} Chandalia et al demonstrated that larger adipocytes in the subcutaneous adipose tissue of South Asian men correlated with IR.³¹ Therefore, both increased visceral adipose tissue and larger adipocytes in the subcutaneous adipose tissue may play a role in the development of IR in South Asians by the adipose tissue function as an endocrine organ, increasing the risk of diabetes.

Biomarkers—Adipose tissue secretes adipokines that have metabolic consequences and further increase the risk of diabetes in South Asians.

Adiponectin is thought to play a role in the modulation of glucose and lipid metabolism in insulin sensitive tissues and decreased circulating adiponectin levels have been implicated in the pathogenesis of IR and diabetes.³² Compared to Caucasians, Asian Indian men have lower levels of adiponectin independent of body fat content and distribution.³³ Lower levels of adiponectin correlate with insulin resistance; Asian Indians with diabetes have the lowest adiponectin levels.^{33,34} There is an inverse correlation between adiponectin and resistin, a pro-inflammatory cytokine³⁴.

Leptin, another hormone produced by adipocytes, is known to have insulin sensitizing and anorexigenic effects.³⁵ However, obese patients develop hyperleptinemia and become leptin resistant, which suppresses insulin action and contributes to IR.³⁵ Compared to Caucasian men, Asian Indian men have higher leptin levels irrespective of body composition.³³ Leptin levels are higher in South Asians with diabetes than those with impaired glucose tolerance and normal glucose tolerance.³⁴

C-reactive protein (CRP) is a pro-inflammatory marker that is associated with an increased risk of diabetes and cardiovascular disease.^{36,37} CRP levels are higher in South Asians compared to Europeans which is accounted for by central obesity and insulin

resistance.^{38,39} Nondiabetic Asian Indian men have higher degrees of IR and higher levels of high sensitivity (hs)-CRP compared to Caucasian men, implying that a pro-inflammatory state is contributing to the increased risk of diabetes in this population.⁴⁰ Mohan et al showed that in an urban south Indian population, hs-CRP levels were higher in diabetic individuals and values increased with increases in tertiles of hemoglobin A1c and body fat.⁴¹ Therefore, CRP does seem to provide a link between adiposity and diabetes. These biomarkers may serve as clinical diagnostic tools in the future.

Genetic Risk Factors—Given the increasing prevalence of diabetes in South Asians, it is important to understand the underlying genetic predisposition. Genome-wide association studies have led to the discovery of approximately 60 genes associated with diabetes risk.⁴²

In South Asians, several polymorphisms have been discovered that are associated with risk factors that predispose to diabetes – including insulin resistance,^{43–46} pancreatic β -cell function,^{47–54} adiposity,^{44,47,49,50,55–64} and the metabolic syndrome.^{65–68} There are several polymorphisms in South Asians that are associated with type 2 diabetes.^{43,47–49,51,56,57,69} (Table 1) The EpiDREAM study investigated whether a gene score (calculated based on 16 single nucleotide polymorphisms (SNPs) associated with diabetes) could help predict the risk of incident type 2 diabetes.⁷⁰ They found that South Asians have a greater genetic load for type 2 diabetes compared to Europeans and Latinos (12% increased risk for each additional SNP vs. 8%) but the gene score adds only marginal information when combined with clinical risk factors.⁷⁰ Regardless, understanding the genetic underpinnings of type 2 diabetes and associated risk factors in South Asians will further elucidate the pathophysiology and potentially modifiable risk factors of diabetes in this high-risk population.

Lifestyle Factors

The Role of Urbanization and Migration—Rapid urbanization and migration with subsequent lifestyle changes have been implicated in the rising rates of diabetes in South Asians.⁷¹

Singh et al showed that urban subjects in Moradabad, India had a higher prevalence of diabetes compared to rural subjects (7.9% vs 2.5%), comparable to the rates observed in migrants to the U.K.⁷² The urban subjects also had a higher prevalence of dyslipidemia and the men had a greater WHR.⁷² A study in southern India showed that villages had the lowest prevalence of diabetes (9.2%) compared to 18.6% in the city and 16.4% in the town.⁷¹ Over time, there has been an increased prevalence of diabetes even in the villages.⁷¹ Therefore, urbanization is associated with an increased risk of diabetes. This was demonstrated by Ramachandran et al where a sedentary lifestyle was an important predictor of diabetes.⁷³

Migration of South Asians to affluent countries like the U.S. results in a high prevalence of diabetes.^{74,75} Migrant South Asians from Gujarat in the U.K. had greater dietary energy intake, fat intake, cholesterol, triglycerides, non-esterified fatty acids and CRP than in non-migrants but diabetes prevalence was high in both populations.⁷⁶

Diet—The typical South Asian diet has several dietary imbalances: low intake of monounsaturated fatty acids, polyunsaturated fatty acids, and fiber and high intake of saturated fats, carbohydrates and trans-fatty acids.⁷⁷ These dietary imbalances are associated with IR and dyslipidemia.⁷⁷ Urbanization and migration have further exacerbated the effects of this imbalanced diet. In a population survey comparing rural and urban subjects in North India, Singh et al showed that urban subjects ate more total and saturated fat, cholesterol and refined carbohydrates and fewer total and complex carbohydrates compared to rural subjects, and had a higher prevalence of diabetes and dyslipidemia.⁷²

Evaluation of diet in Indian migrants to the US has shown that consumption of fruit juice, chips, margarine, cola, and alcoholic beverages has increased regardless of length of time in the U.S.⁷⁸ However, longer term U.S. residents have decreased their consumption of high fat products too such as ghee (clarified butter), butter and milk.⁷⁸ The Oslo Immigrant Health study found that the majority of Sri Lankan migrants to Norway had increased their consumption of meat, milk, butter, margarine and potatoes and about half of the Pakistani migrants had increased consumption of oil, meat, fish and potatoes.⁷⁹ Both groups reported a decrease in bean and lentil consumption.⁷⁹ Increased consumption of these calorie- and energy-rich foods increases the risk of developing IR and subsequently diabetes.⁸⁰

Physical Inactivity—Physical activity is known to be effective in delaying and/or preventing the onset of type 2 diabetes.^{81–83} However, with urbanization and migration, South Asians have been participating in less physical activity. A population survey of rural and urban dwellers in North India showed that energy expenditure during routine and spare time physical activity was higher in rural subjects.⁷² A systematic review from the U.K. showed that South Asians were participating in up to 50–75% less physical activity compared to their European counterparts.⁸⁴

These low levels of physical activity have adverse consequences in South Asians. In a study of an urban South Indian population, prevalence of diabetes increased significantly with a decrease in physical activity and HOMA-IR was higher in those who did light-grade activity compared with heavy-grade activity.⁸⁵ Similarly, in a migrant South Asian population in the U.K., Europeans were found to be more physically active than all South Asian groups and level of physical activity inversely correlated with blood glucose and insulin along with other components of the metabolic syndrome.⁸⁶

Macrovascular Complications of Diabetes (Table 2)

With the increasing prevalence of diabetes in South Asians,^{1–3,87} diabetes-related cardiovascular disease is expected to have a large health and economic burden amongst the South Asian population.

Coronary Artery Disease (CAD)

South Asians, with a 3-fold higher prevalence of diabetes, have an increased incidence of CAD compared to Europeans.⁸⁸ In an 11-year follow-up study of diabetic individuals in the U.K., South Asians were 3.8 times more likely to report a history of myocardial infarction

(MI).⁹ However, the U.K. Prospective Diabetes Study 32 did not detect a difference in rates of MI between South Asians and white Europeans.⁸⁹ Although it is important to point out that the study authors state that there are potential biases that may have led to this finding including: the fact that they excluded subjects who had an MI in the year before diagnosis of diabetes and therefore South Asians included in this study may have been at a lower risk of MI to start with, that this may reflect a shorter duration of diabetes, and finally that the better socioeconomic status of South Asians in this particular study may have placed them at a lower risk of MI than the general diabetic South Asian population.⁸⁹ Similarly, in a large diabetes registry in Northern California, incidence of MI was similar between South Asians and Whites, and much higher than other U.S. ethnic groups.⁹⁰ Regardless, larger and longer term studies are needed to determine if South Asians are at increased risk for MI and CAD compared to other ethnic groups. However, diabetic South Asians have increased mortality from cardiovascular disease.^{8,9,91} Studies investigating the mortality of South Asian with diabetes post-MI have had conflicting results. Wilkinson et al^{92,92} found that South Asians in London had a higher risk of death in the six months post-MI which was attributed to the higher prevalence of diabetes in the group.⁹² On the other hand, a large retrospective cohort study from Canada showed that at median follow-up of 3.5 years, South Asians actually had a lower mortality rate compared to their Canadian counterparts.⁹³

Many studies have been done to determine what risk factors predispose diabetic South Asians to mortality from CAD. Game et al investigated the applicability of the Framingham equation to a population of South Asian diabetes patients and found that the 10-year CAD risks were similar in South Asians and white Caucasians in the U.K.⁹⁴ However, factors contributing to the risk differed in the two ethnic groups with South Asians having lower high-density lipoprotein (HDL) levels and higher total: HDL cholesterol ratios.⁹⁴ The authors proposed that different management of risk factors may account for the higher mortality from CAD in diabetic South Asians. However, there remain reservations about the applicability of the Framingham risk score and other scoring systems for South Asians as other studies have shown that they grossly underestimate the risk.⁹⁵ In addition, reference ranges that have been developed for various metabolic parameters have been derived using Western populations and therefore, may not apply to South Asians.⁹⁵ However, some have proposed adding 10 years to the age of South Asian patients' results in a reasonably accurate measure of CAD risk.⁹⁵

The pathophysiology and genetics behind increased CAD incidence and mortality in diabetic South Asians has been studied. Deepa et al found that urban South Indian diabetic individuals with CAD had increased platelet activation, as measured by collagen induced glycoprotein (GP) IIb/IIIa binding, compared to non-diabetic South Asians without CAD.⁹⁶ Furthermore, results of a regression analysis showed that increased platelet activation was associated with CAD even after adjustment for HbA1c.⁹⁶ Paraoxonase 1 (PON1) is an esterase that protects against oxidative modification of low-density lipoprotein and apolipoprotein A5 (APOA5) is an important determinant of plasma triglyceride levels⁹⁷. Polymorphisms in both genes (see Table 2) were associated with CAD in diabetic South Indians.⁹⁷ Mannose-binding lectin (MBL) activates the lectin pathway of complement activation which causes vascular damage and hence atherosclerosis.⁹⁸ A study of type 2 diabetic South Asians in the Netherlands followed for 8 years showed that low MBL levels

were associated with cardiovascular events.⁹⁸ Oxidative stress plays a role in the development of atherosclerotic plaque and subsequent ulceration and thrombosis.⁹⁹ NADPH oxidase and poly (ADP-ribose) polymerase-1 (PARP1) play a role in the formation of reactive oxygen species (ROS) and cellular dysfunction and death and polymorphisms in these genes can contribute to CAD and MI.⁹⁹ Several pathophysiologic mechanisms exist which may explain the increased incidence of and mortality from CAD in South Asian diabetics.

Cerebrovascular Disease

Several studies have shown the strong association between diabetes and stroke in South Asians. South Asians suffer most commonly from lacunar strokes which suggests small vessel disease attributed to the greater diabetes prevalence in South Asians.¹⁰⁰ A U.S. study found that South Asians with cerebrovascular events were 3-fold more likely to have intracranial atherothrombosis and had a greater prevalence of diabetes compared to European-Americans.¹⁰¹ A community-based study in Pakistan demonstrated an overall 4.8% prevalence of stroke and 11.6% prevalence of diabetes, however the prevalence of diabetes in the stroke population was much higher at 33.3%.¹⁰² Finally a study in Qatar of patients with ischemic stroke, 32% of whom were South Asian showed that diabetes was present in 46.4% of South Asians.¹⁰³ South Asians experience increased mortality from stroke compared to Europeans which also has been associated with diabetes.^{100,104} Results of the West Birmingham Stroke Project found that mortality in migrant South Asians with ischemic stroke was associated with diabetes.¹⁰⁵ Carotid intimal medial thickness (CIMT) is known to be a marker of atherosclerosis and a predictor of cardiovascular disease morbidity and mortality, including stroke.^{106,107} In South Asians living in India, the US and Canada, diabetes has also been strongly associated with higher CIMT.^{87,106,108} In a Canadian study, every 0.9% increase in HbA1c was associated with a 0.026 mm increase in CIMT and the curvilinear relationship was most evident at HbA1c levels > 5.7% among South Asians.¹⁰⁶ The Chennai Urban Rural Epidemiology Study showed that even among those with normal glucose tolerance, increasing HbA1c was associated with significant increases in CIMT (mean CIMT of 0.651 mm for HbA1c <5.2% compared to CIMT of 0.738 mm for HbA1c >5.8%).¹⁰⁷ Elevated homocysteine levels play a role in inflammation and the development of subclinical atherosclerosis.¹⁰⁹ The methylenetetrahydrofolate reductase (MTHFR) gene is involved in the metabolism of homocysteine and the C677T polymorphism is associated with increased homocysteine levels in South Asians.¹⁰⁹

Researchers have begun to study pathophysiologic mechanisms that can explain this association. In a study of South Asians stroke patients in the U.K., Gunarathne et al showed that glycemic status was independently associated with impaired endothelial function and increased arterial stiffness, both mechanisms worse among diabetic subjects.¹¹⁰ Glycemic status impacts production of nitric oxide by the endothelium leading to decreased vascular smooth muscle relaxation and increased arterial stiffness.¹¹⁰ In South Asians with ischemic stroke, there was a clustering of thrombotic factors (tissue plasminogen activator – t-PA, plasminogen activator inhibitor 1 – PAI-1, and fibrinogen) in those who had insulin resistance.¹¹¹ Therefore, glycemic status negatively impacts vascular function and increases thrombosis, both mechanisms observed in South Asian stroke patients.

Peripheral Arterial Disease (PAD)

PAD is an important complication of diabetes and South Asians with diabetes have higher rates of PAD. Diabetic South Asians in the U.K. had significantly higher ankle pressures compared to non-diabetic individuals.¹¹² In the Chennai Urban Population Study, the prevalence of PAD (ankle-brachial index [ABI] < 0.9) in those with normal glucose tolerance, impaired glucose tolerance and diabetes was 2.7, 2.9 and 6.3% and those with known diabetes had a 7.8% PAD prevalence compared to 3.5% in those newly diagnosed with diabetes.¹¹³ South Asians tend to have more distal PAD which may be due to the higher diabetes prevalence and hence the predilection for smaller vessels.¹¹⁴

However, South Asians seem to have lower rates of PAD compared to Europeans. In a study of European and Asian Indian men with a range of coronary disease, Asian Indians had less lower limb atherosclerosis and femoral intimal medial thickness for a given level of coronary disease and established risk factors did not explain this difference.¹¹⁵ Diabetic South Asians in the U.K. had ankle pressures that are similar to those of diabetic Europeans who were 10 years older.¹¹² The Northwest Diabetes Foot Study showed that South Asians were less likely to have PAD compared to Europeans (9% vs 24%) and also had a lower risk of amputation.¹¹⁶ South Asians were also found to have a lower risk of diabetic foot ulcers compared to Europeans – prevalence 5.5% vs 1.8% which was partly attributed to the lower rate of PAD.¹¹⁷

Why this difference exists is not well understood. Some have hypothesized that due to early mortality from cardiovascular disease, South Asians do not live long enough to develop significant PAD.^{112,114,116} Also, different vascular beds may respond differently to diabetes depending on the ethnicity of the patient.^{112,114} Finally, less smoking in the South Asian population may partially explain the lower rates of PAD.^{116,117} Studies to elucidate the biologic mechanisms behind the lower rates of PAD in diabetic South Asians are warranted.

Microvascular Complications of Diabetes (Table 3)

South Asians newly diagnosed with type 2 diabetes have a higher prevalence of microvascular complications at the time of diagnosis compared to Europeans – 27.3% vs. 16.5%, including retinopathy and nephropathy.⁷ Therefore, it is critical to understand the natural history of these complications in South Asians.

Diabetic Retinopathy (DR)

Diabetic retinopathy is a progressive disorder of the microcirculation of the retina and is the most common microvascular complication of diabetes.^{118,119} Retinopathy leads to visual impairment and is one of the leading causes of blindness.¹¹⁸ Sight-threatening retinopathy includes proliferative retinopathy, severe non-proliferative retinopathy and clinically significant macular edema.¹¹⁹

Several studies have demonstrated that South Asians have a higher prevalence of DR compared to Caucasians. Over 11 years of follow-up in the Southall Diabetes Survey, laser treatment for DR was more common in South Asians compared to Europeans – 36% vs. 27%.⁹ In a diabetes clinic in the U.K., South Asians had three-fold higher odds of having

sight-threatening retinopathy (STR) compared to Caucasians.¹²⁰ And for the same level of retinopathy, compared to South Asians, Caucasians were 12.5 years older and had diabetes for 12.5 years longer suggesting that South Asians develop DR at a younger age and earlier in the course of disease.¹²⁰ The AdRem study found that 46% of South Asians had DR compared to 31% of Caucasians.¹¹⁸ Similarly, the U.K. Asian Diabetes Study Retinopathy Study Group found that compared to Europeans, South Asians had a significantly higher prevalence of DR (45% vs. 37%) and STR (16% vs. 12%).¹²¹ Similarly, the DRIVE UK study found higher prevalence of DR (42% vs. 38%) and STR (10% vs. 6%) in South Asians vs. Europeans.¹¹⁹

DR is not the only complication in this group. Retinal vascular lesions such as focal arterial narrowing and arteriovenous nicking are also seen in diabetes and are markers of subclinical vascular disease.¹¹⁸ The AdRem study found that compared to Caucasians, South Asians had a higher prevalence of venous beading (6.3% vs. 2.1%) and arteriovenous nicking (8.5% vs. 7.5%).¹¹⁸ South Asians also had higher prevalence of visual impairment compared to white Europeans in the DRIVE UK study – 6.9% vs. 3.3%.¹²²

These data highlight the importance of understanding the risk factors associated with DR in South Asians. In a cross-sectional study of diabetic South Indians, duration of diabetes, HbA1c, male gender, macroalbuminuria and insulin therapy were independent risk factors for severity of DR.¹²³ Raymond et al found that South Asians with DR tended to have higher systolic and diastolic blood pressure, HbA1c, total cholesterol and younger age at diagnosis.¹²¹ The same was noted in South Asians with retinal vascular lesions.¹¹⁸ Therefore, intensive control of these modifiable risk factors may help to decrease the prevalence of DR and its complications in South Asians.

Researchers are beginning to understand the genetic underpinnings of DR in South Asians. Several genes have been implicated including insulin-like growth factor 1 (IGF-1), endothelial nitric oxide synthase (eNOS), vascular endothelial growth factor (VEGF), inducible nitric oxide synthase (iNOS), tumor necrosis factor β (TNF β), and aldose reductase (ALR2).^{124–127} IGF-1 triggers a cascade of molecular events that initiate retinal angiogenesis and in a diabetic South Indian cohort, the frequency of the 18 cytosine-adenine repeat genotype was higher in those with DR suggesting that it is a susceptibility genotype for DR.¹²⁴ The eNOS gene is involved in hypoxia-induced angiogenesis and therefore is thought to play a role in retinopathy associated neovascularization.¹²⁵ Certain genetic polymorphisms of VEGF have been associated with DR, however no association was seen in a South Indian cohort.¹²⁶ Aldose reductase activity is increased in hyperglycemia.¹²⁷ In mice, knocking out iNOS leads to protection against DR.¹²⁷ And TNF β leads to an increase in vascular cell adhesion molecules which leads to recruitment of inflammatory cells to the site of vascular injury.¹²⁷ Specific allelic variations in each of these three genes were associated with susceptibility to DR in a South Indian cohort (Table 3).¹²⁷

Diabetic Nephropathy (DNP) – Albuminuria and Chronic Kidney Disease (CKD)

Nephropathy is yet another complication of diabetes and CKD from diabetes is the leading cause of end-stage renal disease worldwide.¹²⁸ Albuminuria, an early measure of nephropathy, is an independent predictor of cardiovascular and all-cause mortality.¹²⁹

Ethnicity also influences the risk of DNP. Early studies showed that diabetics of Asian origin have much higher rates of end-stage renal failure compared to Caucasians^{130,131} and they are 5.8 times more likely to accept renal replacement therapy.¹³² Therefore, a better understanding of the risk factors for and pathophysiology of DNP in South Asians is critical.

Many studies have shown that the prevalence of nephropathy – both albuminuria and CKD is higher in the South Asian population. In a cross-sectional study in the UK, prevalence of microalbuminuria was greater in South Asians compared to Europeans (40% vs. 33% in men and 33% vs. 19% in women).¹³³ South Asians had poorer glycemic control and more hypertension although this did not entirely account for the difference.¹³³ In the UKAD study, the proportion of South Asians with microalbuminuria was three times higher compared to white Europeans even with normal blood pressure.¹²⁹ The prevalence of proteinuria was 21% in South Asians compared to 14% in Whites.¹³⁴ Chandie Shaw et al found that South Asians were four times more likely to develop albuminuria compared to Europeans and that loss of GFR was 1.45 times higher in South Asians after five years of follow-up.¹³⁵ Therefore, South Asians also have faster progression of their renal failure.

The prevalence of CKD in South Asians with diabetes is high. Stage 3 CKD was more prevalent in Whites compared to South Asians but stage 4–5 CKD was more common among South Asians.¹³⁴ Indo-Asians had an almost 40-fold increased risk of end-stage diabetic nephropathy compared to the native Dutch population.¹³⁶

Understanding the pathophysiology of DNP in South Asians is important in preventing onset of the disease and delaying its progression. The renin-angiotensin-aldosterone system (RAAS) plays an important role in diabetic kidney disease.¹²⁸ Angiotensin II serves as a potent vasoconstrictor and causes an increase in intraglomerular pressure which results in proteinuria and glomerulosclerosis.¹²⁸ Polymorphisms in the angiotensinogen, aldosterone synthase, chymase and angiotensin II receptor (AGTR1) are associated with diabetic CKD and DNP in Asian Indians.^{128, 137}

Cytokines also play an important role in the development of diabetic CKD.¹³⁸ Transforming growth factor β 1 (TGF β 1) induces renal hypertrophy and fibrosis while cytokines like TNF α and monocyte chemoattractant protein-I (MCP-I, also known as CCL2 or chemokine (C-C motif) ligand 2), whose effects are mediated by chemokine receptors – CCR2 and CCR5, mediate infiltration of macrophages into the kidney.¹³⁸ Interleukin-8 (IL-8) is another chemokine produced by macrophages that has been found in the urine of patients with DNP and is associated with inflammatory renal injury.¹³⁹ Matrix metalloproteinase 9 (MMP9) is a collagenase that is involved in the breakdown of extracellular matrix (ECM), therefore, under expression or decreased affinity for ECM can lead to excess accumulation of ECM and renal damage.¹³⁹ Polymorphisms in these genes can induce glomerulosclerosis and interstitial fibrosis, hence increasing risk of CKD. Studies have discovered several polymorphisms in these genes that are associated with diabetic CKD and increased risk of DNP in Asian Indians (see Table 3).^{138, 139}

Another mechanism hypothesized to play a role in diabetic CKD is the dopaminergic pathway since dopamine is a natriuretic hormone that is involved in the regulation of blood

pressure and salt-water reabsorption in the kidney.¹⁴⁰ Dopamine levels are determined by catechol-O-methyltransferase (COMT), the enzyme that metabolizes dopamine.¹⁴⁰ Dopamine receptors also influence components of the RAAS, and polymorphisms in dopamine receptor-2 and COMT are significantly associated with susceptibility to CKD in diabetic Asian Indians.¹⁴⁰

The oxidative stress pathway plays a role in the development of diabetic complications. In a case-control study of South and North Indians, researchers found that in oxidative stress pathway genes, there is differential genetic susceptibility to diabetic CKD in South Indians and North Indians (see Table 3).¹⁴¹ Another study found that polymorphisms in the receptor for advanced glycation end products (RAGE) and glutamine:fructose-6-phosphate amidotransferase (GFPT2) genes were associated with diabetic CKD in Asian Indians.¹⁴² Interaction between RAGE and its ligands leads to pro-inflammatory gene activation while expression of GFPT in mesangial cells leads to increased sclerosis by upregulating transcription of TGF β 1 and increase the risk of CKD.¹⁴²

Polymorphisms in the acetyl-coenzyme A carboxylase beta (ACAC β) and carnosine dipeptidase 1 (CNDP1) genes are also associated with DNP risk in South Asians.^{137,143} The ACAC β gene is involved in fatty acid metabolism and expression of this gene can lead to accumulation of free fatty acids in cells and hence lipotoxicity.¹³⁷ The product of the CNDP1 gene is important for the breakdown of carnosine which is a ROS expressed in the human kidney and decreased gene expression can lead to nephropathy.¹⁴³

Diabetic Neuropathy (DNU)

Neuropathy is a very debilitating complication of diabetes and increases the risk of foot ulcers which may end up requiring amputations, especially among patients with underlying PAD.

In a South Indian population, prevalence of DNU in patients attending a diabetes clinic was 19%.¹⁴⁴ The Chennai Urban Rural Epidemiology Study showed that the prevalence of DNU was 26%.¹⁴⁵ Risk factors associated with DNU included age, duration of diabetes and glycosylated hemoglobin.^{144,145}

Interestingly, the risk of DNU and its complications are lower in South Asians compared to Caucasians. The UK Prospective Diabetes Study Group showed that Asian Indians with newly diagnosed diabetes had lower rates of neuropathy (4% vs. 13%) diagnosed using the vibration sensation threshold.¹⁴⁶ Abbott et al found that Asian Indians have significantly less large and small fiber neuropathy compared to Europeans.¹⁴⁷ The North-West Diabetes Foot Care Study showed that significantly fewer South Asians had abnormal vibration sensation and abnormal temperature sensation.¹¹⁷ Other studies have also shown that South Asians have significantly less neuropathy than Europeans.^{116,148} The lower prevalence of neuropathy has been attributed to shorter height, less smoking and more favorable skin microcirculation.¹⁴⁷

Accompanying the lower risk of neuropathy, South Asians also have a lower risk of diabetes-related amputations and foot ulcers.⁹⁰ Between 1980–1985, the rate of lower

extremity amputation was lower in Asians compared to Caucasians – 3.4 vs. 14.2 cases per 10,000 patients/year.¹⁴⁹ Data from the Northwest Diabetes Foot Study showed that South Asians had a significantly lower odds of both amputation and foot ulcer when compared to Europeans.^{116,117} The lower risk of these complications is partly attributed to the lower prevalence of neuropathy in the South Asian population as well as less smoking, lower prevalence of PAD, less insulin use and lower prevalence of foot deformities.^{116,117}

Detection and Prevention of Diabetes in South Asians

Given the rising prevalence of diabetes in the South Asian population and the morbidity and mortality associated with diabetes and its complications, strategies to detect and prevent the onset of diabetes are important.

Detection of Diabetes

There are multiple diabetes risk scores^{150,151}, however, these have not been validated in South Asians. Using both urban and rural populations in India, investigators developed and validated the Indian Diabetes Risk Score (IDRS) to detect undiagnosed diabetes in Indians.¹⁵² The score takes into account age, sex, waist circumference, physical activity and family history and can be calculated on-line (<http://www.drmohansdiabetes.com/>), with a score of ≥ 60 out of 100 considered high risk.¹⁵² This score has not been tested against other existing diabetes risk scores. However, one notable difference between the American Diabetes Association (ADA) risk score and the IDRS is that the IDRS uses waist circumference instead of BMI which is likely a better predictor of diabetes risk in South Asians. Therefore, the IDRS can serve as a cost-effective screening tool in South Asians that can be implemented on a large scale and easily identify modifiable risk factors.¹⁵³

Prior Studies of Prevention

Studies focusing on diabetes prevention in South Asians have had promising results and translation of these findings to the community is likely to have a significant impact. The Indian Diabetes Prevention Programme-1 (IDPP-1) was a randomized controlled trial of 531 South Asians recruited from the workplace with impaired glucose tolerance (IGT, mean age 45.9 years) that studied the effect of metformin and lifestyle modification on progression to diabetes.¹⁵⁴ Participants were followed for a median of 30 months and the 3-year cumulative incidence of diabetes were: 55% in the control group, 39.3% in the lifestyle modification group, 40.5% in the metformin group and 39.5% in the combined lifestyle modification and metformin group.¹⁵⁴ The number needed to treat to prevent one incident case of diabetes was 6.4 for lifestyle modification, 6.9 for metformin and 6.5 for combined lifestyle modification and metformin.¹⁵⁴ Therefore, both metformin and the lifestyle interventions were successful in reducing the incidence of diabetes although there was no added benefit from combining them. Snehalatha et al went on to show that these beneficial outcomes occurred due to improved insulin action and sensitivity caused by the intervention strategies.¹⁵⁵

A follow-up study, the IDPP-2, was done to evaluate the effects of pioglitazone.¹⁵⁶ The study included 407 subjects with IGT (mean age 45.3 years) who were randomized to

pioglitazone 30 mg or placebo with lifestyle modification in both arms and followed for 3 years for diabetes.¹⁵⁶ There was no significant difference in diabetes incidence between the two groups – 29.8% in the pioglitazone group and 31.6% in the placebo group.¹⁵⁶ In contrast to other positive studies of thiazolidinediones,¹⁵⁷ this finding may suggest an ethnicity-related difference.

The United Kingdom Asian Diabetes Study (UKADS) was a cluster randomized controlled trial of 1,486 South Asians with type 2 diabetes that investigated the effectiveness of a culturally sensitive, enhanced care package in U.K. general practices in improving cardiovascular risk factors over 2 years.¹⁵⁸ The intervention included additional time with the practice nurse and support from a link worker and diabetes-specialist nurse.¹⁵⁸ While the intervention was not cost-effective, they did demonstrate significant decreases in systolic and diastolic blood pressure and cholesterol across the whole study population attributed to the use of anti-hypertensives and statins.¹⁵⁸ While the clinical outcomes of this study were modest and glycemic control did not improve, the study suggests that intensive management can be effective in this population although significant work to enhance effectiveness of healthcare delivery remains to be done.¹⁵⁸

Ongoing Studies of Prevention

There are several ongoing studies investigating methods to prevent diabetes in South Asians. In India, the Diabetes Community Lifestyle Improvement Program (D-CLIP, Clinical Trials Registry No; NCT 01283308) study is an ongoing randomized trial evaluating the effectiveness, cost-effectiveness, and sustainability of a culturally appropriate lifestyle intervention and metformin in diabetes prevention in high-risk individuals in Chennai, India over 3 years of follow-up.¹⁵⁹ The results of this study will help frame policy and public health recommendations.

In the U.K., the Prevention of Diabetes and Obesity in South Asians (PODOSA) study is an ongoing cluster, randomized controlled trial evaluating the effects of weight loss and increased physical activity in preventing the onset of type 2 diabetes in a high-risk Indian and Pakistani population.¹⁶⁰ The intervention is intensive counseling with 15 dietician visits, with weight change over 3 years being the primary outcome.¹⁶⁰

In the US, the South Asian Health and Prevention Education (SHAPE, Clinical Trials Registry No; NCT 01084928) study is evaluating the effectiveness of a culturally appropriate lifestyle intervention in the prevention of diabetes in the South Asian community with pre-diabetes.¹⁶¹ The intervention is based on the Diabetes Prevention Program but tailored to the needs of the community based on feedback gathered from focus groups.¹⁶¹ Participants are being followed for two years and the primary outcome is weight change.¹⁶¹

Results from these ongoing studies and prior studies will aid in making recommendations for diabetes prevention in South Asians and eventually lead to the development of large scale prevention programs.

Conclusion

The epidemic of diabetes in South Asians is expected to rise over the next several years with India projected to have largest diabetic population in 2030.¹ South Asians have several underlying risk factors that predispose them to diabetes including increased insulin resistance, increased visceral adiposity despite a non-obese BMI, impaired β -cell function, an abnormal adipokine profile and certain high risk genetic polymorphisms. In addition, urbanization and migration have led to detrimental lifestyle changes affecting diet and physical activity. The underlying biologic and genetic predisposition in combination with the lifestyle changes have ignited this epidemic of diabetes. Mortality in South Asians with diabetes is higher than that of other ethnic groups, primarily due to cardiovascular disease. Compared to Caucasians, South Asians have an increased incidence of CAD and cerebrovascular disease but a lower incidence of PAD, which is not entirely understood. In terms of microvascular complications, compared to Caucasians, South Asians have an increased incidence of retinopathy and nephropathy but a lower incidence of neuropathy which is also not well understood. Research is underway to understand the biologic mechanisms and genetic polymorphisms that are playing a role in the development of these diabetes complications. Given the great economic and health burden of diabetes and its complications in South Asians, the focus should be on prevention. Lifestyle modification and metformin therapy have been proven to prevent or delay diabetes in South Asians. Several ongoing studies are investigating the effectiveness of different culturally appropriate lifestyle interventions.^{159–161} We are optimistic that the results of these studies will help to foster changes in public health and health policy and thereby help to reduce the incidence of diabetes and its complications in the South Asian community worldwide.

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Table 1

Genetic Polymorphisms Implicated in Diabetes and Associated Risk Factors

Risk Factor	Gene	Polymorphism	References
Insulin Resistance (IR)	Growth factor receptor-bound protein 14 (GRB14)	rs3923113 (lower insulin sensitivity)	43
	Melanocortin-4 receptor (MC4R)	rs12970134 (higher IR)	44
	Proprotein convertase 1 (PC-1)	K121Q (higher IR)	45
	Vitamin D receptor (VDR)	rs1544410 (BsmI), rs7975232 (ApaI) and rs731236 (TaqI) (*in South Asian women, BsmI BB, ApaI AA, TaqI tt – lower IR; BsmI bb, ApaI aa, TaqI TT – higher IR)	46
Pancreatic β -cell function	Peroxisome proliferator-activated receptor gamma 2 (PPARG)	rs1801282 (associated with HOMA- β , protects against T2DM)	47–50
	Transcription factor-7-like 2 (TCF7L2)	rs10885409 and rs7903146 (associated with HOMA- β , lower insulin secretion)	47–49, 51
	ST6-galactosamide α -2,6-sialyltransferase (ST6GAL1)	rs16861329 (lower pancreatic β -cell function)	43
	Hepatocyte nuclear factor 4 α (HNF4A)	rs4812829 (lower pancreatic β -cell function)	43
	Potassium voltage-gated channel, KQT-like subfamily, member 1 (KCNQ1)	rs2237897 , rs2237892 , rs2283228 , rs231362 and rs2237895 (Bolded – not statistically significant, associated with HOMA- β and β -cell dysfunction)	49, 52, 53
	Cell division cycle protein 123 homolog (CDC123/CAMKID)	rs12779790 (*in Sikhs, lower fasting insulin, impaired β -cell function)	54
Adiposity	Fat-mass obesity associated (FTO)	rs1421085, rs8050136 and rs9939609 (specifically BMI, waist circumference and waist-to-hip ratio in North Indians)	47, 49, 55–59
	Melanocortin-4 receptor (MC4R)	rs12970134 (specifically waist circumference)	44
	Lipoprotein lipase (LPL)	-T93G; and -G53C (protects against obesity)	60
	Uncoupling protein-3 (UCP3)	-55C \rightarrow T (*influences waist-to-hip ratio in South Indian women)	61
	Peroxisome proliferator-activated receptor gamma 2 (PPARG)	rs1801282 (associated with obesity)	62
	Tumor necrosis factor- α (TNF α)	Gly308Ala (associated with obesity)	62
	Adiponectin (ADIPOQ)	rs12495941 (*in Sikhs – associated with total body weight and waist and hip circumference – not statistically significant)	50
	Perilipin (PLIN)	14995A>T (associated with obesity)	63

Risk Factor	Gene	Polymorphism	References
	Uncoupling protein-2 (UCP2)	-866G/A (*specifically central obesity)	64
Metabolic syndrome	Fatty acid binding protein 2 (FABP2)	Ala54Thr and Thr54Thr (lower risk of metabolic syndrome)	65–66
	Apolipoprotein A1 (APOA1)	T655C, T756C and T1001C (lower risk of metabolic syndrome)	67
	Lipoprotein lipase (LPL)	S477X (*Metabolic syndrome LESS frequent)	68
Other (Type 2 diabetes)	Insulin-like growth factor 2 binding protein 2 (IGF2BP2)	rs4402960	47–49
	Transcription factor-7-like 2 (TCF7L2)	rs12255372	51
	Fat-mass obesity associated (FTO)	rs7193144, rs9940128 , rs11076023 and rs1588413 (Bolded – in South Indians)	56–57
	Potassium inwardly-rectifying channel, subfamily J, member 11 (KCNJ11)	rs5219	48
	Solute carrier family 30 (zinc transporter), member 8 (SLC30A8)	rs13266634 and rs11558471	48–49
	Hematopoietically expressed homeobox (HHEX)	rs1111875	48–49
	Cyclin-dependent kinase inhibitor 2A (CDKN2A)	rs10811661	48–49
	CDK5 regulatory subunit associated protein 1-like 1 (CDKAL1)		
	Vacuolar protein sorting 26 homolog A (VPS26A)	rs1802295	43
	High mobility group 20A (HMG20A)	rs7178572	43
	Adaptor-related protein complex 3, σ 2 subunit (AP3S2)	rs2028299	43
	Peroxisome proliferator activated receptor- γ co-activator-1 α (PGC-1 α)	Thr394Thr (G \rightarrow A)	69
	Insulin-receptor substrate 1 (IRS-1)	rs2943641	49
	JAZF zinc finger 1 (JAZF1)	rs864745	49
	Kruppel-like factor 14 (KLF14)	rs972283	49
	Dual specificity phosphatase 9(DUSP9)	rs6945326	49
Coiled-coil-helix-coiled-coil-helix domain containing 9 (CHCHD9)	rs13292136	49	

Table 2

Mechanisms and Genes Implicated in Macrovascular Disease

Complications of Diabetes	Mechanisms and Genes	Polymorphism (if applicable)	References
Coronary artery disease	Increased platelet activation	N/A	96
	Paraoxonase1 (PON1) (South Indians)	192RR	97
	Apolipoprotein A5 (APOA5) (South Indians)	1131CC	97
	Low mannose-binding lectin (North Indians)	O/O genotype	98
	NADPH oxidase p22phox (South Indians)	C242T	99
Cerebrovascular disease	Poly (ADP-ribose) polymerase-1 (PARP-1)(South Indians)	Val762Ala	99
	Increased arterial stiffness	N/A	110
	Poor endothelial function	N/A	110
	Clustering of thrombotic factors (PA, PAI-1, fibrinogen)	N/A	111
	Methylenetetrahydrofolate reductase (MTHFR) (associated with increased carotid intimal medial thickness)	677T/T, associated with increased plasma homocysteine	109
Peripheral arterial disease	Not well studied		

Table 3

Mechanisms and Genes Implicated in Microvascular Disease

Complications of Diabetes	Mechanisms and Genes	Polymorphism (if applicable)	References
Diabetic retinopathy (South Indians)	Insulin-like growth factor 1 (IGF-1) gene	18 cytosine-adenine repeat genotype	124
	Aldose reductase (ALR2) gene	Z+2 allele	127
Diabetic nephropathy	Inductible nitric oxide synthase (iNOS) gene	13-repeat (CCTTT) genotype	127
	Tumor necrosis factor β (TNF β) gene	15-repeat (GT) genotype	127
	Angiotensinogen	Met235Thr SNP	128
	Aldosterone synthase	T>C (-344) SNP	128
	Chymase	G>A (-1903) SNP	128
	Angiotensin receptor II, type 1 (AGTR1)	rs5186 SNP	137
	Dopamine receptor-2 (DRD2)	141 ins/del C and G>A SNPs	140
	Catechol-O-methyltransferase (COMT)	900 ins/del C SNP	140
	Chemokine (C-C motif) ligand 2 (CCL2)	rs3917887 SNP	139
	Chemokine receptor-5 (CCR5)	59029 G>A SNP	138-139
	Matrix metalloproteinase 9 (MMP9)	rs17576 SNP	139
	Carnosine dipeptidase 1 (CNDP1)	5/5 homozygous genotype (lower frequency)	143
	Receptor for advanced glycation end- products (RAGE)	-429 T>C SNP	142
	Glutamine-fructose-6-phosphate transaminase 2 (GFPT2)	rs7725 (C>T SNP in 3' UTR)	142
Acetyl-coenzyme-A carboxylase beta (ACAC β)	rs2268388 SNP	137	
In South Indians			
Superoxide dismutase 2 (SOD2)	Wild-type allele (Ala9Val)		141
Uncoupling protein 1 (UCP1)	-112 T>G and Ala64Thr SNPs		141
Endothelial nitric oxide synthase 3 (NOS3)	Glu298Asp SNP		141
Glutathione-S-transferase P1 (GSTP1)	Ile105Val		141
In North Indians			
Vascular endothelial growth factor (VEGF)	-460 T>C SNP		141
Paraoxonase1 (PON1)	Arg192Gly SNP		141
Interleukin-8 (IL-8)	rs4073 SNP		139
Chemokine receptor-5 (CCR5)	DD polymorphism		139

Complications of Diabetes	Mechanisms and Genes	Polymorphism (if applicable)	References
Diabetic neuropathy	Not well studied		