Basal Insulin and Cardiovascular and Other Outcomes in Dysglycemia

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Diabetes in Asia

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Prevalence of type 2 diabetes has rapidly increased in native and migrant Asian populations. Diabetes develops at a younger age in Asian populations than in white populations, hence the morbidity and mortality associated with the disease and its complications are also common in young Asian people. The young age of these populations and the high rates of cardiovascular risk factors seen in Asian people substantially increase lifetime risk of cardiovascular disease. Several distinctive features are apparent in pathogenetic factors for diabetes and their thresholds in Asian populations. The economic burden due to diabetes at personal, societal, and national levels is huge. National strategies to raise public awareness about the disease and to improve standard of care and implementation of programmes for primary prevention are urgently needed.

Introduction

Diabetes and associated complications pose a major health-care burden worldwide and present major challenges to patients, health-care systems, and national economies (panel 1). WHO estimates that between 2000 and 2030, the world population will increase by 37% and the number of people with diabetes will increase by 114%.[1] Asia is the major site of a rapidly emerging diabetes epidemic.[1,2] Conservative estimates based on population growth and ageing and rate of urbanisation in Asia show that India and China will remain the two countries with the highest numbers of people with diabetes (79·4 million and 42·3 million, respectively) by 2030.[1] Additionally, among the top ten countries, four more are in Asia—Indonesia, Pakistan, Bangladesh, and the Philippines. Prevalences are probably underestimated because changes due to other diabetes-related risk factors have not been considered.

The world population is expected to reach 7·9 billion by 2025. Six countries account for almost 50% of the population increase every year; among them, three Asian countries, India, China, and Pakistan, contribute 21%, 12%, and 5%, respectively.[3] Asian populations are racially heterogeneous and have differing demographic, cultural, and socioeconomic characteristics. Differences in genetic and environmental attributes affecting diabetogenesis could also be heterogeneous. We discuss type 2 diabetes in Asian countries other than Japan.

Epidemiology

In 2003, an estimated 194 million adults worldwide had diabetes (5·1%) and 314 million people had impaired glucose tolerance (8·2%).[4] These prevalences increased to 6·0% and 7·5% in 2007 and are predicted to increase to 7·3% and 8·0% by 2025.[2] 380 million people are expected to have diabetes in 2025.[2] 85–95% of all diabetes cases are of type 2 in developed countries and this percentage is even higher in developing countries.[2] Roughly 80% of people with diabetes are in developing countries, of which India and China share the largest contribution. Prevalence estimates (adjusted to world population) of diabetes and impaired glucose tolerance in all Asian countries are high and are expected to increase further during the next two decades.[2]

The increase is likely to be most substantial in developing countries that are undergoing the most rapid economic growth. The gross domestic product per head in India and China is lower than in some other Asian countries, despite increases of three and five times, respectively, over the past two decades (figure 1). The increases in diabetes prevalence in India and China are especially alarming compared with more developed regions within Asia, showing a mismatch between affluence and diabetes prevalence—an Asian diabetes paradox. Epidemiological data from Asian countries draw attention to the high prevalence of type 2 diabetes in urban and rural populations (table 1).[2,5–38] Prevalence of impaired glucose tolerance is high in many Asian countries, suggesting the presence of a large pool of people with potential to develop diabetes.[2] In southeast Asia, the estimated prevalence of impaired glucose tolerance was 6·0% in 2007.[2] The rapidly increasing rate of diabetes in Asia is associated with a strong gene–environmental interaction, which is propelled by lifestyle changes caused by modernisation. Migrant Asian groups have a higher susceptibility to adverse environmental influences than do co-inhabitants of different races.[39]

Pathophysiology

Asian populations are multiracial and have multifactorial causes of type 2 diabetes. The mechanisms underlying development of the disease are complex and varied, even within these populations. The major

Search strategy and selection criteria

We searched PubMed using the keywords "diabetes in developing countries", "diabetes in Asia", "type 2 diabetes in Asia", "risk of diabetes in Asian populations", "obesity and diabetes in Asians", "genetics of type 2 diabetes in Asian populations", "Chinese", "polymorphisms", and "adipokines and diabetes in Asian populations". Peer-reviewed reports published between 1980, and 2009, in English and Chinese were included. Several International Diabetes Federation and WHO publications were used, in addition to reviews and book chapters. We also searched the reference lists of reports identified by the search strategy and selected those judged relevant.

aetiological components of type 2 diabetes are impaired insulin secretion and impaired insulin action, which are aggravated by the presence and degree of glucotoxicity. Both components might also be genetically predetermined. Lipotoxicity plays an important part in causing insulin resistance and β-cell damage.[40] In the natural history of type 2 diabetes, β-cell function undergoes a series of changes. With the development of obesity and other adverse effects on insulin sensitivity, β cells respond with compensatory hyperinsulinaemia. Such changes are seen even in non-diabetic people with strong familial history of diabetes.[41] With increasing duration, β-cell function declines and insulin-to-glucose ratio diminishes, before an ultimate decompensation occurs with expression of clinical diabetes. Asian populations are more insulin resistant than are people of many other races.[42–45] Insulin resistance and compensatory hyperinsulinaemia are reported even in children and adolescents of Asian Indian origin.[46,47] These factors probably play a major part in the escalating prevalence of type 2 diabetes in young populations in Asia.

Risk factors for diabetes show substantial racial and geographical variations in expression and intensity. The escalating prevalence of diabetes and cardiovascular diseases in developing countries is mostly related to environmental changes. Asian populations have several important characteristics with respect to biological and environmental risk factors for diabetes (panel 2).

Genetic factors

Type 2 diabetes has a strong genetic component and most Asian patients have a first-degree relative with diabetes.[48,49] Much progress has been made in our understanding of the genetics of this disease. Importantly, most of the loci originally associated with diabetes in European populations have been replicated in Asian populations. Whereas monogenic forms of diabetes result from rare genetic mutations with large effects, such as those seen in maturity-onset diabetes of young people,[50] most cases of type 2 diabetes are thought to be due to genetic variations that are more common but exert less effect. In early studies, genetic variants in the peroxisome proliferator-activated receptor-γ gene (PPARG)[51] and the ATP-sensitive potassium channel Kir6·2 (KCNJ11) were reproducibly associated with type 2 diabetes.[52] In Asian populations, the protective effect of the PPARG*A12Ala allele on insulin resistance and risk of type 2 diabetes was not consistently seen.[53] Polymorphisms in the gene encoding transcription-factor-7-like protein 2 (TCF7L2) was reported to be associated with type 2 diabetes in 2006.[54] With a combined odds ratio of 1·46 for the rs7903146 variant,[55] this gene has the strongest effect on type 2 diabetes. However, the at-risk T allele in rs7903146 is rare, and different genetic variations in TCF7L2 are associated with type 2 diabetes in Asian populations.[56,57]

Panel 1: Burden of type 2 diabetes

- Prevalence of diabetes is rising worldwide.
- The incidence is highest in developing countries, especially in Asia.
- Among Asian countries, India and China have the highest numbers of people with diabetes.
- The high prevalence and large population size contribute to the huge burden of diabetes on these countries.
- The poorest economic strata bear the highest cost burden of diabetes treatment.
- The economic cost increases many times with the development of vascular complications.
- Developing countries need to increase national capacity for early diagnosis, encourage effective management, and improve primary prevention to combat the rising burden due to this chronic disease.

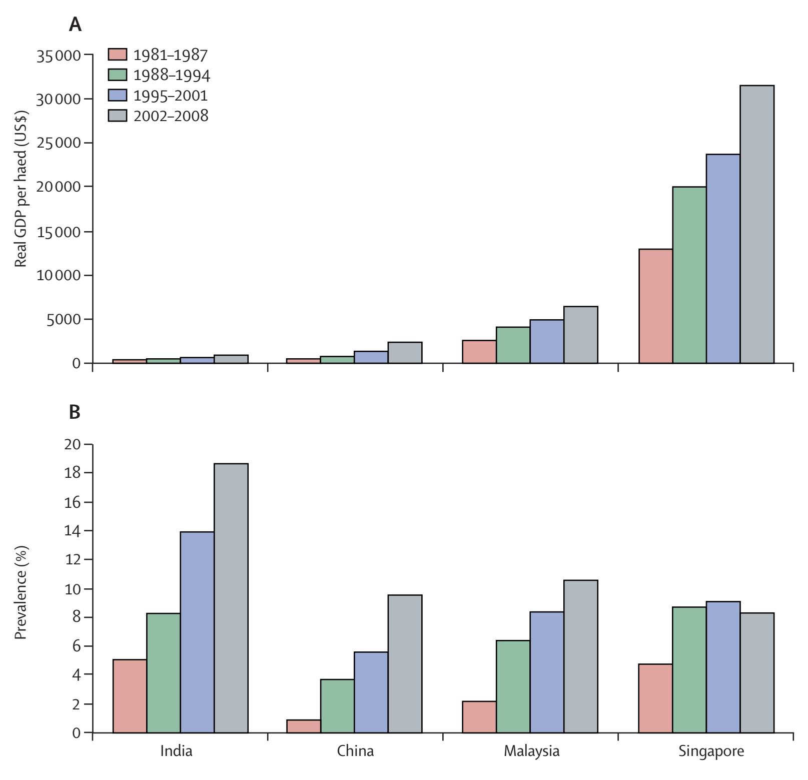

Figure 1: **Economic development and prevalence of diabetes in selected Asian countries, 1981–2008**
(A) Real gross domestic product per head. Data from the US Department of Agriculture Economic Research Service (http://www.ers.usda.gov/Data/Macroeconomics/Data/HistoricalRealPerCapitaIncomeValues.xls, accessed April 28, 2009). (B) Prevalence of diabetes. Data derived from table 1. GDP=gross domestic product.

Several other genetic variants have been identified through genome-wide association studies, which is a strategy that uses the genotyping of hundreds of thousands of single-nucleotide polymorphisms on a single array. These variants are associated with type 2 diabetes in different Asian groups, including Chinese, Japanese, Korean, and Indian populations (table 2).[53–74]

	Prevalence			Number of people with diabetes[2] (×10³)		Urbanisation[5]	
	National	Urban	Rural	2007	2025*	1990	2010
India							
2006[6]	..	18·6%	9·2%	40850·8	69881·6	25·5%	30·1%
2003[7]	..	14·3%	..				
2000[8]	12·1%	13·5%	..				
1995[9]	..	11·6%	..				
1989[10]	..	8·2%	2·4%				
1985[11]	..	5·0%					
China							
2004[12]	..	..	9·5%	39809·6	59269·7	27·4%	44·9%
2002[13]	6·1%	6·9%	5·6%				
2001[14]	5·5%†	..	..				
1997[15]	3·2%						
1994[16]	2·5%	..	..				
1986[17]	0·8%	..	..				
1980[18]	1·0%	..	..				
Hong Kong							
1996[19]	9·8%	..	..				
1990[20]	4·5%	..	..				
Taiwan							
1996[21]	9·8%	..	..				
Korea							
2001[22]	7·6%†	..	..	3073·8	4163·3	73·8%	81·9%
Thailand							
2004[23]	6·7%†	..	..	3162·4	4660·2	..	..
2000[24]	9·6%‡	..	..				
Pakistan							
2006[25]	..	10·6%	7·7%	6929·5	11537·6	30·6%	37·0%
1995[26]	..	16·3%	9·3%				
Bangladesh							
2005[27]	..	8·1%	2·3%	3848·1	7419·2	19·8%	28·1%
2000[28]	..	..	3·8%				
1997[29]	..	4·5%	..				
Singapore							
1998[30]	9·0%	..	..	384·8	692·4	100·0%	..
1992[30]	8·6%	..	..				
1984[30]	4·7%	..	..				
Malaysia							
1999[31]	..	10·5%	..	1530·6	2742·9	49·8%	72·2%
1996[32]	..	8·3%	..				
1986[32]	..	6·3%	..				
1982[32]	..	2·1%	..				

(Continues on next page)

A meta-analysis showed that, although risk alleles of the different variants seem to confer similar risk for type 2 diabetes in European and Asian populations, ethnic differences in their frequencies lead to differences in population-attributable risk, showing the need for population-specific studies.[65] Two recent Japanese genome-wide association studies replicated several loci previously identified in Europeans, and reported variants in the *KCNQ1* gene that are associated with type 2 diabetes in Japanese and other east Asian populations.[73,74]

Most genetic variants associated with type 2 diabetes seem to be related to insulin secretion rather than insulin resistance, and several of the risk alleles are associated with reduced islet-cell function[58,59,68,73,75,76] (table 2 and figure 2). One of the variants, *FTO*, is associated with changes in fat mass and predisposes to diabetes via the effects of obesity; it is the first common variant to be associated with obesity and diabetes in European as well as Asian populations. However, by contrast with European groups, the association in Asian populations is not entirely mediated through body-mass index.[77] Mechanisms linking body size with type 2 diabetes seem to vary between Indian and European populations. Several other variants have been linked to obesity, although none has so far been associated with diabetes. The present catalogue of type 2 diabetes risk variants probably accounts for only a small proportion of the genetic basis of type 2 diabetes. Nevertheless, the identification of these variants has provided insights into pathogenesis of type 2 diabetes.

Urbanisation and migration

Rates of urbanisation are variable, but substantial increases in urbanisation will occur in most Asian countries[5] (table 1). By 2010, the proportion of urbanisation will be more than 50% in Singapore, Korea, Malaysia, the Philippines, and Indonesia, and more than 30% in China, Pakistan, India, and Thailand. The remaining countries (Bangladesh and Sri Lanka) have slow rates of urbanisation. Increasing urbanisation is due to natural population growth and expansion of urban areas. It is also affected by rural to urban migration.[78] The expected increase in urban population would be a main determinant, besides ageing, of the rise in the global prevalence of diabetes. Data from Asian countries show the effect of urbanisation on diabetes prevalence.[5–38] Physical activity decreases and body-mass index and upper-body adiposity increase substantially with urbanisation.[79] Internal rural to urban migration results in similar adverse changes. Most Asian countries, in particular India and China, are experiencing rapid socioeconomic progress and are susceptible to such consequences.

The prevalence of diabetes is increasing in urban and rural populations in both India and China, although prevalence is substantially higher in India than in China (table 1 and figure 1). A nationwide study done in China in 2000 revealed that 7·3% of the population are affected by impaired glucose tolerance, with striking rural–urban differences.[14] Importantly, only 30% of the 20 million people estimated to have diabetes on the basis of fasting plasma glucose had previously been diagnosed.[14] These findings suggest that China is still in the early stages of an evolving diabetes epidemic. The prevalence will probably rise further as China continues to develop economically and becomes increasingly urban.[80] This conclusion is supported by higher prevalence rates in

Chinese populations in Hong Kong and Taiwan than in their mainland counterparts.[80]

Urban lifestyles cause enormous changes in diet, physical activity, and health. Urban populations eat more diverse diets and more macronutrients and animal food than do rural residents, but with higher intake of refined carbohydrates, processed foods, and saturated and total fat and lower intake of fibre. Increasing incomes partly account for these differences, but such changes are evident at any income.[81] The effect of nutrition transition is large and most of the emerging epidemic of chronic disorders, such as diabetes, cardiovascular diseases, stroke, and hypertension, are diet related.

Migration to more affluent countries results in high prevalence of diabetes in many populations. This effect is seen, for example, in Asian Indian migrants,[39,42] Chinese groups from mainland China,[82] and Japanese migrants[82] to several other countries. The rise in prevalence is a result of environmental and behavioural changes and not due to changed gene frequencies, since the increases have occurred within a few decades.

	Prevalence			Number of people with diabetes[2] (×10³)		Urbanisation[5]	
	National	Urban	Rural	2007	2025*	1990	2010
(Continued from previous page)							
Philippines							
2004[33]	6·5%	··	··	3055·1	5572·7	48·8%	66·4%
Sri Lanka							
2006[34]	10·3%	16·4%	8·7%	1186·6	1786·2	17·2%	15·1%
1995[35]	··	8·1%	··				
Vietnam							
2001[36]	3·8%†	6·9%§	··	1294·6	2500·7	30·3%	28·8%
1993[36]	2·5%	··	··				
Indonesia							
1992[37]	··	5·7%§	··	2887·8	5129·0	30·6%	53·7%
Cambodia							
2005[38]	··	11·0%	5·0%	326·2	608·1	12·6%	22·8%

*As projected by WHO. †Based on fasting plasma glucose. ‡Estimated prevalence. §Crude prevalence.

Table 1: **Prevalence of diabetes, number of people with diabetes, and percentage of urbanisation in Asian countries**

Age

The results of the Diabetes Epidemiology Collaborative Analysis of Diagnosis Criteria in Asia (DECODA) study have shown several variations in age-specific prevalence within Asian populations.[83] In Indian populations, the prevalence of diabetes peaks at 60–69 years of age, whereas in Chinese populations it peaks at age 70–89 years. Indian people have higher age-specific prevalence and higher prevalence of impaired glucose regulation at a younger age than do Chinese people.[83] Findings from India,[6] Pakistan,[25] and Sri Lanka[34] are similar. These differences are probably related to environmental and genetic influences.

One of the hallmarks of diabetes in Asian countries is the rapidly increasing prevalence of young-onset diabetes. A high prevalence of maturity-onset diabetes in the young has been reported in India.[84] In China, from 1994 to 2000, there was an 88% increase in prevalence in the 35–44 years age group.[14] Data from southern India show that the prevalence of diabetes in people younger than 44 years has increased from 25·0% of the total prevalence in 2000 to 35·7% in 2006.[6,8] Factors that have contributed to the epidemic of obesity and young-onset diabetes are the rapid transition in dietary habits, reduced physical activity, changing pattern in leisure activities, longer working hours, and decreasing sleep hours.[80,85,86] Asian people with young-onset diabetes have substantial phenotypic heterogeneity, many with positive family history, impaired β-cell function, no islet autoantibodies, and coexistence of cardiometabolic risk factors.[49,87] This tendency to impaired β-cell secretory function might be due to genetic factors, although visceral adiposity and lipotoxicity, low birthweight and maternal imprinting,[88] β-cell loss and amyloid deposits might also have contributory roles.[80,89]

Type 2 diabetes in children is increasing at an alarming rate, especially in Asian children in both native lands and in migrant populations.[90] Its prevalence in the UK is 14 times higher in Asian children than in white European children.[91] Population-based and community-based studies of type 2 diabetes in children are few,[92] but several clinic-based studies have been done.[87,90] The epidemic of type 2 diabetes in children is expected to become worse with the increasing rate of obesity in children in developing countries.[90] The 2002 National Nutrition and Health Survey in China showed that 4·1% of children aged 7–12 years and 5·6% of children aged 12–18 years were overweight, and the respective obesity prevalences were 2·5% and 1·6%.[93] In Hong Kong, the results of a community-based study showed that 8–10% of children aged 12–13 years were obese.[94]

Adipose tissue and insulin resistance

The prevalence of insulin resistance and metabolic syndrome is high in Asian people.[95] Features of insulin resistance are manifested in children and adolescents of south Asian origin even in the absence of obesity.[46,47] Obesity is a major determinant of type 2 diabetes, and is associated with many metabolic aberrations that impair insulin sensitivity.[96,97] These abnormalities include excess lipolysis causing increased concentrations of non-esterified fatty acids and triglycerides in blood and skeletal muscle. Glucose uptake by muscle is suppressed. Obesity also impairs insulin action by changing secretion of cytokines, specifically of leptin and adiponectin,[98] and leads to proinflammatory conditions.[99] Features of insulin resistance, including hypertriglyceridaemia[100,101] and increased abdominal or visceral fat,[43–45] are seen even in non-obese Asian populations. Insulin resistance has been studied extensively in Asian Indian

Panel 2: Characteristics of risk factors for type 2 diabetes in Asian countries

- Most Asian countries are undergoing a socioeconomic transition.
- Increasing levels of modernisation, industrialisation, and economic advancements adversely affect biological and environmental risk factors for diabetes.
- Asian populations have low thresholds for conventional risk factors such as age, body-mass index, upper-body adiposity.
- Adverse effects on health are manifested on pre-existing genetic predisposition, insulin resistance, and other metabolic features, at a younger age in Asian populations than they are in white populations.
- Diabetes develops at least a decade earlier in Asian than in white people. Prevalence of young-onset diabetes is increasing in Asian populations.
- Young-onset diabetes and type 2 diabetes in children are common and their rising trend is linked to epigenetic factors, such as maternal imprinting, and to unhealthy lifestyle changes leading to high rates of obesity.
- Both the thrifty genotype and thrifty phenotype might be operative in Asian groups.
- These characteristics are heterogeneous in Asian populations.
- These populations also have high rates of clustering of cardiovascular risk factors—ie, metabolic syndrome even at a young age.

groups. Hyperinsulinaemia, a characteristic of insulin resistance, is common in Asian people, especially in southeast Asian populations.[43–45]

Unusually, Asian Indian groups have high concentrations of non-esterified fatty acids in plasma during fasting despite relative hyperinsulinaemia, and this concentration is not suppressed by oral glucose administration.[43] They also concomitantly have high plasma leptin and low plasma adiponectin concentrations. These changes are independent of obesity or intra-abdominal fat distribution. With development of obesity, these abnormalities will be aggravated.[42,43]

Asian people generally have a lower body-mass index than do people of many other races, but the association between body-mass index and glucose intolerance is as strong as in any other population. Asian populations seem to differ from European populations in associations between body-mass index and percentage of body fat and health risks. On the basis of the evidence, a WHO expert consultation concluded that a substantially increased risk of type 2 diabetes and cardiovascular diseases occurs at body-mass index lower than 25 kg/m². However, for Asian populations there is no uniform threshold for body-mass index to identify people who are overweight and obese. Although the WHO body-mass index figure should be retained as an international classification, individual countries could make decisions about the definition of increased risk for their populations.[102] WHO recommends that a body-mass index of 18·5–22·0 kg/m² is healthy for Asian people.[102] The International Diabetes Federation criteria for healthy waist circumference for Asian people is less than 90 cm for men and less than 80 cm for women.[103] Revised guidelines for diagnosis of obesity, abdominal obesity, and metabolic syndrome in Asian Indian populations were put forward by a consensus group in India.[104] According to these guidelines, the criteria are a healthy body-mass index of 18·0–22·9 kg/m², an overweight body-mass index of 23·0–24·9 kg/m², and obesity greater than or equal to 25 kg/m². The healthy waist circumference limits are 90 cm for men and 80 cm for women.

Abdominal obesity is a characteristic feature in many Asian populations, especially in southeast Asia. Insulin resistance is associated with visceral and subcutaneous fat content.[105] Young south Asian men in the USA had insulin resistance even without increased intraperitoneal fat mass, unlike the white population studied.[42] The ethnic difference in Asian Indian people could be mostly related to the higher amount of truncal fat and to the large dysfunctional subcutaneous fat cells,[106] rather than to presence of excess visceral fat. Glucose disposal rate and plasma adiponectin concentration are inversely related to fat-cell size. South Asian groups generally have a low rate of glucose disposal and low adiponectin concentrations, but high leptin concentrations.[42] A high proportion of body fat is seen even in newborn babies. A large, prospective study in India has shown that Indian newborn babies are thinner, shorter, and lighter than UK babies, but are relatively fat because of paucity of non-fat tissues.[88]

Fatty acid influx to the liver is an important pathogenetic factor for fatty liver and is also a determinant of excess triglyceride-rich lipoproteins. Dyslipidaemia in type 2 diabetes is more severe in the presence of fatty liver. Ectopic fat accumulation in the liver and skeletal muscle are important determinants of insulin resistance and can also predispose to development of type 2 diabetes.[107] The twin cycle hypothesis put forth in a review by Taylor[108] explains the cycle of reactions linking muscle insulin resistance, ectopic fat deposition in the liver and islets, hepatic insulin resistance, and β-cell dysfunction eventually resulting in onset of type 2 diabetes (figure 3). Such pathogenetic mechanisms are likely to be operating in Asian people who have features of insulin resistance and have been adversely affected by maladaptation to modernisation and affluence.

Low adiponectin concentrations in plasma in Asian people have been linked to low insulin sensitivity and high prevalence of diabetes and cardiovascular diseases.[109] In Asian populations, low adiponectin concentrations are predictive of type 2 diabetes.[110] However, the investigators did not find a direct association between adiponectin and insulin resistance or other

	Chromosome location	Gene function	Marker	Risk allele	OR*	Replicated/discovered marker in Asian populations	Risk allele	OR
PPARG	3	Adipocyte development; target of glitazone class of drugs	rs1801282[58]	C	1·14	Not consistently replicated[53]	..	..
KCNJ11	11	Kir6·2 potassium channel	rs5219[59]	T	1·14	Japanese (rs5219)[60,61]	T	1·25, 1·32
TCF7L2	10	Transcription factor, transactivates glucagon, regulates insulin secretion	rs7903146, rs1225537[54]	T, T	1·37	Indians (rs12255372,[62] rs7903146,[63] rs10885409[64])	T, T, C	1·50, 1·50, 1·64
TCF7L2	10	Transcription factor, transactivates glucagon, regulates insulin secretion	rs7903146[55]	T	1·46	Chinese (rs290487,[56] rs1196205,[65] rs1196218[57])	C, C, G	1·51, 2·11, 1·43
TCF7L2	10	Transcription factor, transactivates glucagon, regulates insulin secretion	..	..	..	Japanese (rs1255372,[66] rs7903146[67])	T, T	1·70, 1·69
SLC30A8	8	Zinc transporter, insulin storage and secretion	rs13266634[58]	C	1·12	Japanese (rs13266634);[60] Chinese and Koreans (rs13266634)[57]	C; C	1·23; 1·13
CDKAL1	6	Islet glucotoxicity sensor, regulates insulin secretion	rs7756992, rs13266634;[68] rs7754840[58]	G, C; C	1·20, 1·15; 1·12	Chinese (rs7756992, rs13266634);[68] Japanese (rs7756992)[60]	G, C; G	1·25, 1·19; 1·16
HHEX	10	Transcription factor in pancreatic development	rs1111875[58]	C	1·13	Japanese (rs1111875);[60] Chinese and Koreans (rs7923837)[57]	C; G	1·24; 1·25
IGF2BP2	3	Growth factor binding protein, pancreas development	rs4402960[58]	T	1·14	Chinese and Koreans (rs4402960);[57] Japanese (rs4402960);[60] Indians (rs4402960)[64]	T; T; T	1·12; 1·37; 1·37
CDKN2A/ CDKN2B	9	Cyclin-dependent kinase inhibitor, islet development	rs10811661[58]	T	1·2	Chinese and Koreans (rs10811661);[57] Chinese (rs10811661);[69] Japanese (rs10811661)[60]	T; T; T	1·27; 1·31; 1·26
FTO	16	Fat mass and obesity associated; alters body-mass index	rs8050136[58]	A	1·17	Indians (rs9939609);[64] Chinese and Koreans (rs8050136)[57]	A; A	1·46; 1·16
WFS1	4	Wolframin. Endoplasmic reticulum transmembrane protein	rs10010131[70]	G	1·15	†	..	..
JAZF1	7	Transcriptional repressor	rs864745[71]	T	1·10	†	..	..
HNF1B	17	Transcription factor, pancreas development	rs757210[72]	A	1·12	†	..	..
CDC123/ CAMK1D	10	Calcium/calmodulin-dependent protein kinase 1D; cell cycle	rs12779790[71]	G	1·11	†	..	..
ADAMTS9	3	Secreted metalloprotease	rs4607103[71]	C	1·09	†	..	..
NOTCH2	1	Transmembrane receptor; pancreatic organogenesis	rs10923931[71]	T	1·13	†	..	..
THADA	2	Thyroid adenoma associated gene; apoptosis	rs7578597[71]	T	1·15	†	..	..
TSPAN8/ LGR5	12	Tetraspanin 8; cell surface glycoprotein	rs7961581[71]	C	1·09	†	..	..
KCNQ1	11	Potassium voltage-gated channel	rs2237892,[73] rs2237895[74]	C, C	1·29, 1·24	Japanese (rs 2237892),[73] Chinese (rs2237892),[73] Korean (rs2237892)[73]	C, C, C	1·43, 1·38, 1·41

Genetic variants with suggestive association with type 2 diabetes but without genome-wide statistical significance are not included. OR=Odds ratio. *Approximate effect size for the variant associated with type 2 diabetes. †No published data.

Table 2: **Replicated type 2 diabetes gene nearest to the identified marker**

cardiometabolic risk variables.[111] A study in migrant south Asian women in the USA[112] had similar findings. The mechanism by which adiponectin is linked with diabetes might also differ in south Asian populations. More detailed studies are needed to explain the mechanisms underlying insulin resistance in these populations.

Asian Indian people produce higher amounts of adenosine triphosphate despite being more insulin resistant, and have higher intramuscular triglyceride concentrations than do white people in the USA.[113] Concentrations of intramuscular triglycerides are similarly high in Asian Indian people with and without diabetes, suggesting a possible difference in the association of insulin resistance and diabetes in this population.[113] Moreover, in Asian Indian populations, plasma triglycerides and non-muscle triglycerides are strongly associated with insulin sensitivity.[114]

A pathophysiological link has been shown between obstructive sleep apnoea and excess visceral fat, independent of overall body fat.[115] Obstructive sleep apnoea might be directly related to insulin resistance in both obese and non-obese people.[116] Physical inactivity and sleep deprivation might also be contributing factors for many of the inflammatory, oxidative, endothelial, and coagulation abnormalities that are associated with obstructive sleep apnoea.[115]

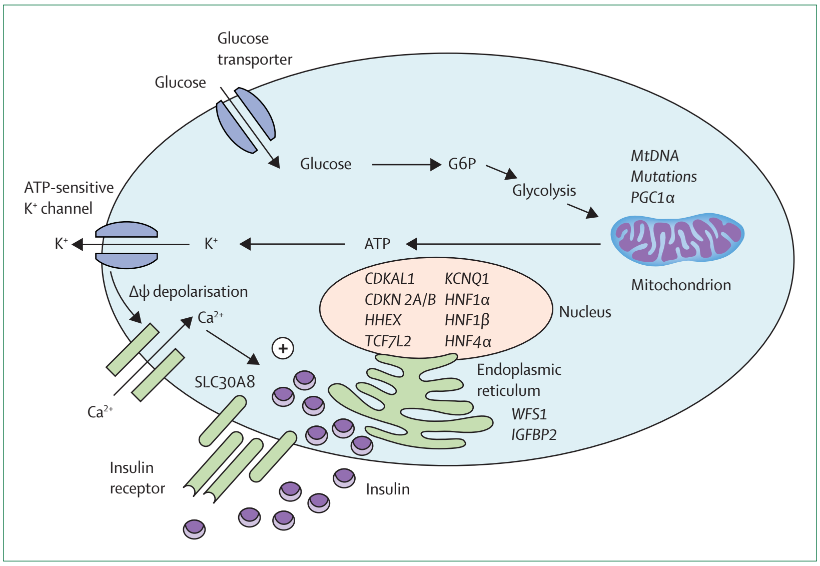

Figure 2: **The role of type 2 diabetes genes in insulin secretion**
Pancreatic β-cell genes associated with type 2 diabetes are in italics. G6P=glucose-6-phosphate. Adapted from Florez JC. Newly identified loci highlight beta cell dysfunction as a key cause of type 2 diabetes: where are the insulin resistance genes? *Diabetologia* 2008; **51:** 1100–10, by kind permission of the author and Springer Science + Business Media.

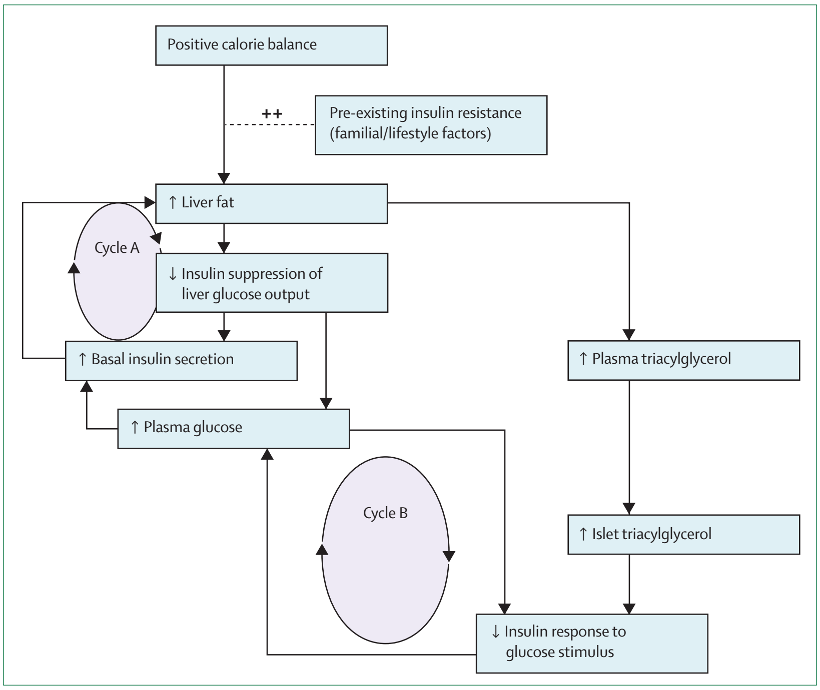

Figure 3: **The twin vicious cycles in pathogenesis of type 2 diabetes[108]**
Cycle A: Development of fatty liver, which leads to increases in basal plasma glucose and basal insulin secretion leading to hepatic insulin resistance. Cycle B: Sequence of changes in tissues when exposed to higher concentrations of triacylglycerols that leads to decreased insulin response to ingested glucose. Postprandial response to glucose becomes blunted. These vicious cycles have inhibitory effects on islet-cell functions leading to a sudden onset of clinical diabetes.

Intrauterine environment and imprinting

Intrauterine and postnatal environment can affect future risk of diabetes and cardiovascular disease via fetal programming.[117] The thrifty genotype and thrifty phenotype hypotheses seem to apply to Asian populations. Maternal undernutrition, infant's low birthweight, and rapid postnatal child growth are all associated with increased risk of diabetes in offspring, and these factors might be especially relevant to developing countries such as India[88] and China.[118] Additionally, offspring of women who are obese or have diabetes are at increased risk of diabetes and other cardiometabolic complications.[117–119] In view of the increase in childhood obesity and increasing number of women with young-onset diabetes in Asia, this link will further exacerbate the situation by creating a vicious cycle of diabetes begetting diabetes.

The mechanism underlying such transgenerational inheritance of disease risk is under intense investigation; it is thought to involve epigenetic silencing of target genes via methylation or histone modification during development, resulting in a mismatch between the metabolic phenotype that was programmed during development and the nutritionally rich adult environment.[117] Again, this mismatch might be most pronounced in countries that are undergoing the most rapid economic development. Improved understanding of the effect of maternal imprinting is needed to help to address the epidemic of diabetes in Asia.

Diagnosis and complications

The latest WHO report on the definition and diagnosis of diabetes recommended that the oral glucose tolerance test be retained as a diagnostic test.[120] The need to identify postprandial hyperglycaemia seems especially relevant in Asian populations. In the DECODA study,[83] more than half the patients with diabetes had isolated postprandial hyperglycaemia, which is also a powerful predictor of cardiovascular disease and premature death.[121] In Asian populations, fasting plasma glucose[83,122] and glycosylated haemoglobin (HbA_{1c}) concentrations[123] have much lower sensitivity than does 2 h postglucose concentration for detection of diabetes.

Owing to the early onset of disease, Asian patients with diabetes are at high risk of developing long-term diabetic complications. In urban areas, prevalence of diabetes is lower in poor socioeconomic strata than in high-income groups, but glycaemic control is poor, so the occurrence of vascular complications is higher.[101,124] Few population-based data are available for vascular complications of diabetes from developing countries. In Asian countries, an estimated 30% of people with type 2 diabetes have retinopathy. In North America, the prevalence of diabetic end-stage renal disease is nearly 80% higher in Asian than in white patients with diabetes; however, rates of below-the-knee amputations are 60–69% lower and the incidence of cardiovascular disease is 24–33% lower.[125] Although the prevalence of peripheral vascular complications is low in Asian Indian people, because of the large population the number with foot complications is high. Prevalence of neuropathy is high and it is a risk factor for foot infections.[126]

High rates of cardiovascular complications have been reported in native and migrant south Asian populations.[127] Heterogeneity in the occurrence of cardiovascular risk variables is manifested in migrant south Asian groups, based on their socioeconomic strata.[127] Possible discrepancies in adjustment for comorbidities might explain the conflicting findings. Within Asia, susceptibility to vascular complications varies. In the WHO Multinational Study of Vascular Disease in Diabetes, Chinese patients with diabetes had much lower rates of coronary artery disease than did patients in other centres, but they had substantially higher rates of retinopathy and nephropathy.[128] A high prevalence of nephropathy was also shown in the results of the Microalbuminuria Prevalence (MAP) study, which noted a prevalence of 40% for microalbuminuria and 20% for macroalbuminuria in hypertensive patients with type 2 diabetes in Asia.[129] In addition to genetic factors, the tendency towards visceral adiposity is also likely to contribute to development of cardiovascular and renal complications.[130]

Health-care outcome

The diabetes health-care situation is similar across most developing countries. Economic disparities, scarcity of adequate health-care facilities, and low educational status prevalent in these countries pose major hurdles for achievement of optimum glycaemic control. The cost of diabetes care is high and is increasing worldwide. The economic burden is very high, especially in developing countries, and more so in the lower economic groups, who spend 25–34% of their income on diabetes care.[131,132] The cost of care increases substantially when complications occur or when admission to hospital, surgery, or insulin treatment is needed. The results of a few studies suggest that treatment of patients with diabetes in developing countries is far from optimum.[133,134]

In the International Diabetes Management Practice Study, investigators analysed diabetes care outcome in urban areas in 18 countries, including eight countries from Asia, and showed that about a third of patients who were treated by diabetologists or endocrinologists had reached the goal of HbA_{1c} concentrations of less than 7%.[134] However, the proportion was similar in other developing regions, namely eastern Europe, Latin America, and Africa. Up to 40% of patients were not screened for risk factors or complications. In developing countries, factors pertinent to patients, doctors, and health-care systems all affect glycaemic control.[134]

Prevention and future action

Prevention of obesity and diabetes is more cost effective than is the treatment of complications resulting from diabetes. A 2–3% reduction in energy intake or an extra 10–15 min of walking each day could offset weight gain in roughly 90% of the population in China.[85] Lifestyle intervention can have a sustained benefit, with a 43% reduction in incidence of diabetes over a 20-year period.[135] The results of a primary prevention study in India have also shown that lifestyle modification is effective with an approximate reduction of 30% in comparison with the control group.[136] Lifestyle modification was the most cost-effective intervention for prevention of diabetes in high-risk groups.[137]

The challenges for diabetes care in India, China, and other Asian countries will include improved education to alert the population to risk factors for diabetes, training of patients to manage their disease more effectively, and development of more structured care delivery and management of cardiometabolic risk factors.[138,139] A mismatch of national health-care budget and health-care burden, especially due to the epidemic of non-communicable diseases, poses a huge challenge in most countries. More data are needed for the economics of diabetes and the quality of life and cost-effectiveness of various interventions. Well targeted basic research is needed to provide insight into feasible strategies for prevention of diabetes and its complications.

A UN resolution has recognised type 2 diabetes as a serious epidemic for which urgent steps to improve management and prevent disease development are needed. It urges member states to develop national policies towards these goals.[140] In many Asian countries (eg, India, China, Pakistan, Bangladesh, Malaysia, Vietnam, and Singapore), governments have initiated national programmes for prevention and control of non-communicable diseases. Programmes targeting greater public awareness of these diseases and strategies to build national capacity by training medical and paramedical personnel to manage the disorders are expected to curb the epidemic.

Contributors

All authors have seen and approved the revised version of the Seminar. AR had final responsibility for the decision to submit for publication.

Conflicts of interest

We declare that we have no conflicts of interest.

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