Genetics of type 2 diabetes mellitus

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Type 2 diabetes mellitus is a heterogeneous disease that is caused by both genetic and environmental factors. Only a minority of cases of type 2 diabetes are caused by a single-gene defect, such as maturity-onset diabetes of youth (mutated *MODY* gene), syndrome of insulin resistance (insulin receptor defect), and maternally inherited diabetes and deafness (mitochondrial gene defect). The genetic component of the more common form of type 2 diabetes is probably complex and involves the interactions of multiple genes and environmental factors. The candidate gene approach has identified several genes that regulate insulin signalling and secretion, but their contributions to diabetes are small. Recent genome scan studies have been conducted to identify major susceptibility loci that are linked with type 2 diabetes. This information would provide new insights into the identification of novel genes and pathways that lead to this complex disease.

Introduction

The maintenance of the blood glucose concentration within a narrow range (between 3 and 7 mmol/L) irrespective of the pathophysiological circumstances, depends on the intricate relationships between the actions of insulin—the only hormone that reduces blood glucose level—and those of counter-regulatory hormones. The latter group of hormones comprises growth hormone, catecholamines, cortisol, and glucagon, all of which tend to elevate blood glucose levels (Fig 1). Insulin reduces the blood glucose level by enhancing glucose uptake, mainly in the muscle and liver, thereby promoting glucose oxidation and glycogen synthesis. Insulin also inhibits lipolysis and hepatic glucose production, and facilitates energy storage by promoting lipogenesis. Type 2 diabetes mellitus is a heterogeneous disease characterised by chronic
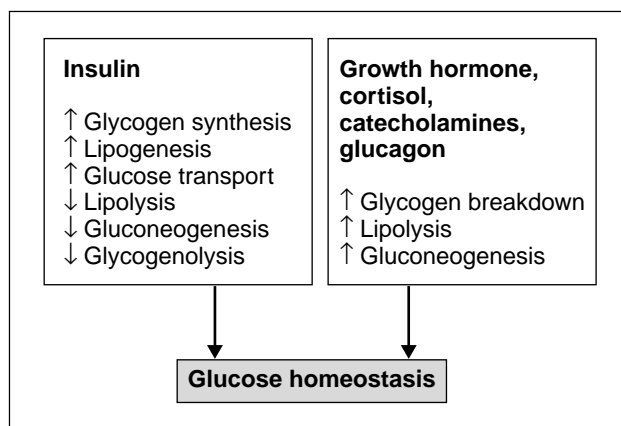

Fig 1. The roles of insulin and counter-regulatory hormones in the regulation of glucose homeostasis

hyperglycaemia owing to a combination of insulin resistance and changed insulin secretion.[1] As a result, there is insufficient insulin action to keep the blood glucose level within normal limits. More than 85% of all cases of diabetes mellitus are type 2 diabetes.[2] This disease affects not only the elderly and middle-aged people, but also increasingly, young people, especially in non-Caucasian populations.

The development of diabetes: nature or nurture?

Genes play an important role in the development of diabetes mellitus, particularly type 2 diabetes.[3] Unlike autoimmune type 1 diabetes mellitus, no clear relationship has been described between the human

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Specific types of diabetes mellitus

(1) Genetic defects of β-cell function
   (a) Chromosome 20, *HNF-4α* (*MODY1*)
   (b) Chromosome 7, glucokinase (*MODY2*)
   (c) Chromosome 12, *HNF-1α* (*MODY3*)
   (d) Chromosome 13, *IPF-1* (*MODY4*)
   (e) Chromosome 17, *HNF-1β* (*MODY5*)
   (f) Mitochondrial DNA mutation
   (g) Others

(2) Genetic defects in insulin action
   (a) Type A insulin resistance
   (b) Leprechaunism
   (c) Rabson-Mendenhall syndrome
   (d) Lipoatrophic diabetes
   (e) Others

(3) Diseases of exocrine pancreas

(4) Endocrinopathies

(5) Drug-induced or chemical-induced diabetes

(6) Infections

(7) Uncommon forms of immune-mediated diabetes

(8) Other genetic syndromes
   (a) Down's syndrome
   (b) Friedreich's ataxia
   (c) Huntington's chorea
   (d) Klinefelter's syndrome
   (e) Laurence-Moon-Biedl syndrome
   (f) Myotonic dystrophy
   (g) Porphyria
   (h) Prader-Willi syndrome
   (i) Turner's syndrome
   (j) Wolfram's syndrome
   (k) Others

leukocyte antigen genes and type 2 diabetes. In studies of monozygotic twins, the concordance rate for type 2 diabetes has been reported to be 90% or more, even in twins with a major difference in body weight.[4] There are also marked racial differences in the prevalence of type 2 diabetes; prevalence rates in populations such as Asians and American Indians are particularly high.[5,6] A minority of cases of type 2 diabetes, such as maturity-onset diabetes of youth (MODY), result from mutations in a single gene.[7] Some specific subgroups of diabetes caused by genetic defects of β-cell function or insulin action have also been described (Box).[3] The majority of cases of type 2 diabetes, however, are multifactorial in origin, and different combinations of several genes that interact with non-genetic factors contribute to the development of hyperglycaemia.[3,8]

The apparent genetic heterogeneity seems surprising in view of the similarity in the pathogenesis of type 2 diabetes in different populations. Hence, the genetic origins of type 2 diabetes may be diverse. The disease may represent maladaptation to and selection of different genotypes in response to different evolutionary pressures, rather than be derived from a common genotype that is present in most populations and which has now been rendered detrimental by changes in lifestyle. Identifying the genetic components of type 2 diabetes not only provides insight into the mechanisms of diabetes, but also allows the identification of susceptible individuals, for whom an early diagnosis can be made and suitable treatment subsequently given.

Insulin resistance

Insulin resistance means an impaired biological response to insulin by one or more of its target tissues, the consequence is reduced glucose disposal in response to insulin. Insulin exerts its biological effect via binding to its receptor, which resides on the cell surface of target tissues.[3] The insulin receptor consists of two α chains and two β chains, which are connected by disulphide bridges. The binding of insulin to one of the extracellular α chains leads to the autophosphorylation of multiple tyrosine molecules in the intracellular domain of the β chain. The phosphorylated receptor then transfers the message inside the cell by phosphorylating tyrosine residues on insulin receptor substrate-1 (IRS-1). This intracellular protein is considered to play a central role in the intracellular signal cascade that is involved in glucose uptake and glycogen synthesis. The IRS-1 also transfers the growth-promoting and mitogenic signals of insulin to the nucleus, thereby stimulating protein synthesis.

Defects in the insulin-signalling pathway, owing to mutations in the insulin receptor gene or the presence of antibodies to the insulin receptor or insulin itself, are rare causes of insulin resistance.[9] Polymorphisms in the *IRS-1* gene have been associated, although not strongly, with insulin resistance in various populations.[10,11] Further support comes from studies of knockout animal models.[12,13] Familial studies in Pima Indians and other populations show the clustering of risk factors related to insulin resistance,[6,14] thus suggesting that genetic factors may contribute to the development of insulin resistance. Other factors such as obesity, postmenopausal state, exercise, drug use (glucocorticoids, β-blockers, and adrenergic agents), and infections may also influence the development of insulin resistance.[1,15]

Most studies show that defective glucose oxidation and glycogen synthesis in muscle are the major causes of insulin resistance in type 2 diabetes.[1,16] These observations may be in part explained by fuel competition—namely, an increased level of free fatty acids competing with glucose as energy substrates.

Increased levels of free fatty acids can also induce insulin resistance by reducing the hepatic clearance of insulin and enhancing gluconeogenesis through the Randle cycle.[17] More recent evidence suggests that long-chain fatty acids may modulate gene transcription or directly affect the activity of glycogen synthase.[18] Furthermore, adipose tissue produces a pro-inflammatory cytokine, tumour necrosis factor α, which can inhibit insulin signalling by inhibiting the phosphorylation of the insulin receptor and IRS-1.[19] Other cytokines such as interleukin-6 may also induce endothelial dysfunction, which in turn can contribute to the clustering of cardiovascular risk factors, as encountered in the metabolic syndrome.[20]

Recent studies have also suggested that poor nutrition in foetal and infantile life, as reflected by a low birthweight, is detrimental to the development and function of pancreatic β cells and insulin-sensitive tissues.[21,22] This 'thrifty phenotype' would eventually lead to the development of diabetes during the normal ageing process or with the onset of obesity. On the other hand, among infants with a low birthweight, those foetuses with the 'thrifty genotype' can store energy as fat more efficiently in an unfavourable intrauterine environment and thereby have a survival advantage. These foetuses, however, have a higher risk of the development of diabetes later in life.[23] These two hypotheses would explain the high prevalence of type 2 diabetes among individuals who had a low birthweight and who have an affluent lifestyle that is characterised by food abundance, physical inactivity, and psychosocial stress.

Although insulin resistance is a strong predictor of type 2 diabetes, insulin resistance alone is not sufficient to cause diabetes. The majority of patients with type 2 diabetes have a moderate degree of insulin resistance.[16] Furthermore, obese non-diabetic individuals who have a moderate degree of insulin resistance do not necessarily become glucose intolerant, thus showing that relative insulin deficiency is essential for hyperglycaemia to develop.[24] Indeed, Mitrakou et al[25] have shown that early-phase insulin secretion—that is, during the first 15 to 30 minutes after a glucose challenge—and the suppression of glucagon secretion are reduced in subjects with impaired glucose tolerance.[25] Once hyperglycaemia has developed, glucose toxicity can induce insulin resistance and decrease pancreatic β-cell function, thus setting up a vicious cycle. Insulin secretion and action are hence closely interconnected, and a defect in one is likely to lead to defect in the other and thereby contribute to the development of late-onset diabetes.[1,26]

Maturity-onset diabetes of youth

Blood glucose is the main secretagogue for insulin secretion. In response to a high blood glucose level, a specific glucose transporter in the β cells, glucose transporter-2, facilitates the uptake of glucose into the cell. Glucose is then phosphorylated by glucokinase to glucose-6-phosphate, the first rate-limiting step in glycolysis. As a result of glycolysis and mitochondrial oxidative phosphorylation, adenosine triphosphate (ATP) is produced and facilitates the closure of the transmembrane potassium channels. The subsequent depolarisation of the cell membrane causes an influx of calcium ions, which stimulates insulin synthesis and the release of presynthesised insulin stored in vesicles.

Maturity-onset diabetes of youth is a subtype of type 2 diabetes and accounts for 2% to 5% of cases of type 2 diabetes.[27] It is characterised by an autosomal dominant inheritance over three generations, onset or recognition at a young age (ie in childhood, adolescence, or young adult life, usually <25 years) and primary defects in insulin secretion.[28] Genetic studies have shown that MODY can be caused by mutations in the genes encoding the glycolytic enzyme glucokinase[29]; three liver-enriched transcription factors expressed in the pancreatic β cell—namely, hepatocyte nuclear factors HNF-1α,[30] HNF-1β,[31] and HNF-4α[32]; and the pancreatic/duodenal transcription factor insulin promoter factor-1 (IPF-1).[33] Physiological studies have shown that heterozygous mutations in these genes have a dominant-negative effect on the normal pancreatic β-cell secretory function.[34] The presence of other familial forms of diabetes that are not associated with gene mutations that are known to cause MODY suggests there are other genes involved in its onset.[27]

Hepatic nuclear factors belong to a group of transcription factors that are distributed in various cell types including the pancreatic β cells, hepatocytes, and kidney cells. In the liver, these transcription factors help regulate the expression of genes that are involved in the metabolism of glucose, cholesterol, and fatty acids. In the pancreas, the same transcription factors regulate the expression of glucose transporters as well as enzymes involved in glucose metabolism. Furthermore, IPF-1 is crucial for the embryonic development of pancreatic islets.[35] The transcription factors form an intimate network, which is shown in Figure 2.[27] Froguel and Velho[27] have recently shown that long-chain fatty acids directly modulate the activity of HNF-4α. This finding has provided an important insight into the mechanism that links free fatty acids to insulin secretion.
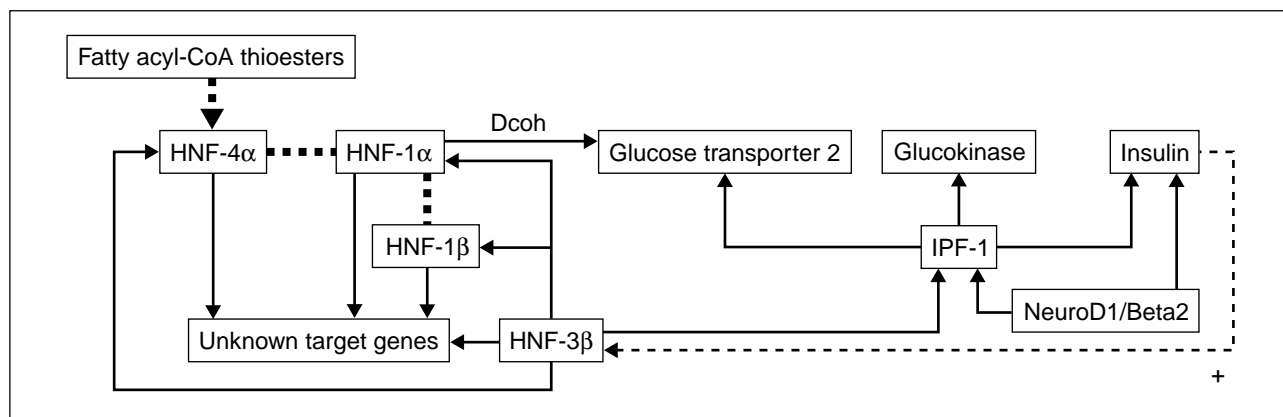
Fig 2. Network of DNA-binding factors involved in transcription in the pancreas[21]
Dcoh is a cofactor of HNF-1α and NeuroD1/Beta 2 is a β-cell transcription factor

Various mutations have been identified in all five genes that are known so far to cause MODY, but a common mutation has not been found in various kindreds. Mutations that have been identified are deletions, insertions, or substitutions of nucleotides, which cause changes in amino acid sequences and possibly protein function. Various phenotypes, which differ in the site and form of mutation, have been described.[36] More than 80 different mutations have so far been identifed in the glucokinase gene, which is situated on chromosome 7p13-15 and which is commonly known as *MODY2*.[36] This form of MODY is also known as MODY2 and is the most well-characterised subtype of MODY. Glucokinase is mainly expressed in pancreatic β cells and in the liver, and it acts as a glucose sensor to fine-tune insulin secretion and the blood glucose level. Patients with glucokinase diabetes tend to present in early childhood with a mild clinical course; diabetic complications are uncommon.[29,37] Defective glucokinase activity leads to a decreased rate of glycolysis in pancreatic β cells, the consequence of which may be an increase in the blood glucose threshold that triggers insulin secretion. Furthermore, there is a decreased accumulation of glycogen and increased rate of gluconeogenesis in the liver following meals.[36] There are marked differences in the prevalence of MODY2 in different populations; the disease accounts for approximately 50% of and 17% of MODY families in France and the United Kingdom, respectively.[38,39]

Patients with mutations in the genes that encode HNF-4α (*MODY1*) or HNF1-α (*MODY3*), which are located on chromosomes 20q12-q13.1 and 12q22-qter, respectively, have altered glucose metabolism in the liver and impaired insulin secretion in the β cells.[40,41] Most patients present at a post-pubertal age and tend to have a more rapidly progressive clinical course. They also often have more severe hyperglycaemia and disease complications.[28,32,42] Approximately 30% of patients with MODY1 require insulin for treatment of their diabetes.[28] MODY2 and MODY3 are the most common forms of MODY in northern Europe and Asian patients,[38,39,43-45] whereas MODY1 is rare.[32]

A homozygous mutation in the human *IPF-1* (*MODY4*) gene has been associated with pancreatic agenesis and the same result has been demonstrated in an embryonic mouse model.[46] In contrast, mutation of the *HNF-1β* (*MODY5*) gene is associated with early renal disease, as shown by the presence of multiple renal cysts in patients with MODY5; early renal disease in MODY5 may even appear before the onset of diabetes.[31] It has been suggested from these observations that HNF-1β plays a role in renal development.[47] Molecular genetic and clinical investigative studies of patients with different forms of MODY have provided important insights into the understanding of the pathophysiology of diabetes and the foundation for clinical studies of pancreatic β-cell function in other forms of diabetes.[48,49]

Mitochondrial diabetes

Mitochondria contain enzymes that participate in the Krebs cycle, and are the major production sites of ATP and the transfer of fatty acids. Mitochondria are thus the main source of cell energy and play critical roles in the maintenance of insulin action and insulin secretion.[50] These organelles contain their own DNA, which encodes some of the mitochondrial components, including ribosomal and transfer RNAs and some respiratory chain proteins. The mitochondrial genome is maternally transmitted because mitochondria in the tail of sperm are not transferred to the oocyte during fertilisation. The maternal preponderance of type 2 diabetes has prompted the investigation of the association between mitochondrial DNA (mtDNA) and diabetes.[51]

The mitochondrial genome is extremely vulnerable to free radical damage, because mtDNA has no histone backbone and there is only a limited DNA repair system in mitochondria. Consequently, the risk of mutation is 10-to 20-fold that of nuclear DNA.[50] The genetic transmission of mtDNA is complex in that it basically follows population genetics with cytoplasmic (thus maternal) inheritance. Transmission is also influenced by nuclear factors as well as the type of tissue, because different tissues contain different amounts of mitochondria, which are randomly partitioned into daughter cells during mitosis. Heteroplasmic cells contain a mixture of wild-type (normal) and mutant mtDNA, but the mtDNA genotype may shift towards being the wild-type only (homoplasmic) or to different degrees of heteroplasmy during cell replications. This process acts as a protective mechanism in which the wild-type mtDNA can compensate for the defective function of the mutant mtDNA.[50] The emergence of diabetes depends on which cells are most affected. Most studies of mtDNA have been performed in peripheral leukocytes; using pancreatic β cells and insulin-sensitive tissues would be more informative.

One can classify abnormal mtDNA in two ways: as qualitative changes (deletion or mutations) or a quantitative decrease (through nuclear mechanisms). These changes can be either inherited or acquired. Mutation or deletion of mtDNA is known to cause various clinical conditions, such as diabetes mellitus, mainly by causing insulin deficiency.[51-53] Maternally inherited diabetes and deafness (MIDD) is a common form of mitochondrial diabetes and is caused by an A→G substitution at position 3243 in the mtDNA-encoded tRNA[Leu(UUR)] gene.[51-53] This form of diabetes is characterised by insulin deficiency, maternal inheritance, and high-tone deafness.[51,52] The frequency of this mutation has been reported to range between 1% and 3% in patients with type 1 or type 2 diabetes in various Asian populations, depending on the selection criteria such as age of onset and the presence of family history.[51,54]

Patients with type 2 diabetes have lower levels of mtDNA in their peripheral blood. This reduction precedes the onset of diabetes, and the mtDNA level correlates inversely with blood pressure and waist to hip ratio. There are also quantitative relationships between mtDNA levels, insulin secretion, and patterns of energy utilisation.[55] These findings suggest that the mtDNA level may be an important determinant of insulin action. The exact nature of the relationship between a low mtDNA level and diabetes is currently not known. However, semi-quantitative inheritance of mtDNA has been observed in mother-baby pairs. Mothers with low mtDNA in their peripheral blood tend to have offspring with low birthweight.[55] Furthermore, the mtDNA content of diabetic offspring is only half of that found in babies without a family history of diabetes.[56] Park et al[57] have shown that the offspring of diabetic rats that have received a protein- and calorie-restricted diet have low levels of mtDNA, insulin resistance, and reduced insulin secretion.[57] Hence, poor mitochondrial biogenesis because of a decreased mtDNA content might be the basis of the heritable 'thrifty phenotype', which is characterised by both insulin resistance and deficiency.

The involvement of the amylin gene in diabetes

Amylin is a biologically active peptide that is predominantly co-secreted with insulin from pancreatic β cells and is the major component of pancreatic amyloid deposits.[58] It can cause insulin resistance in skeletal muscle as well as the death of pancreatic β cells.[59] Furthermore, a study of transgenic mice expressing human amylin found that early-onset diabetes spontaneously developed in homozygote males at 8 weeks. In contrast, diabetes developed in only 20% of the homozygote female animals at 30 weeks. These findings were associated with selective β-cell degeneration and impaired insulin secretion.[60] Crossover of the hemizygote animals with other strains has also resulted in the development of diabetes and β-cell dysfunction.[61] Despite these experimental findings, linkage analysis and population studies do not support the notion that the amylin gene is a major genetic determinant in the pathogenesis of type 2 diabetes.[62]

Studies from Japan, however, have shown that mutation of the amylin gene may play a role in the pathogenesis of early-onset type 2 diabetes.[63] A single heterozygous missense mutation (corresponding to amino acid change S20G in the amylin gene) has been found in 4.1% of Japanese patients with type 2 diabetes and 10% in those patients with an early onset of disease.[63] All the patients required insulin treatment and gave a strong family history of late-onset type 2 diabetes.[63] The authors concluded that the S20G mutation of the amylin gene might cause mild diabetes on its own, but when combined with as yet unidentified susceptibility genes for late-onset type 2 diabetes, the mutation might contribute to the early onset of the disease and increase the severity of the clinical course. In an in vitro study, the Congo red absorption assay was used to show that the S20G-mutated amylin
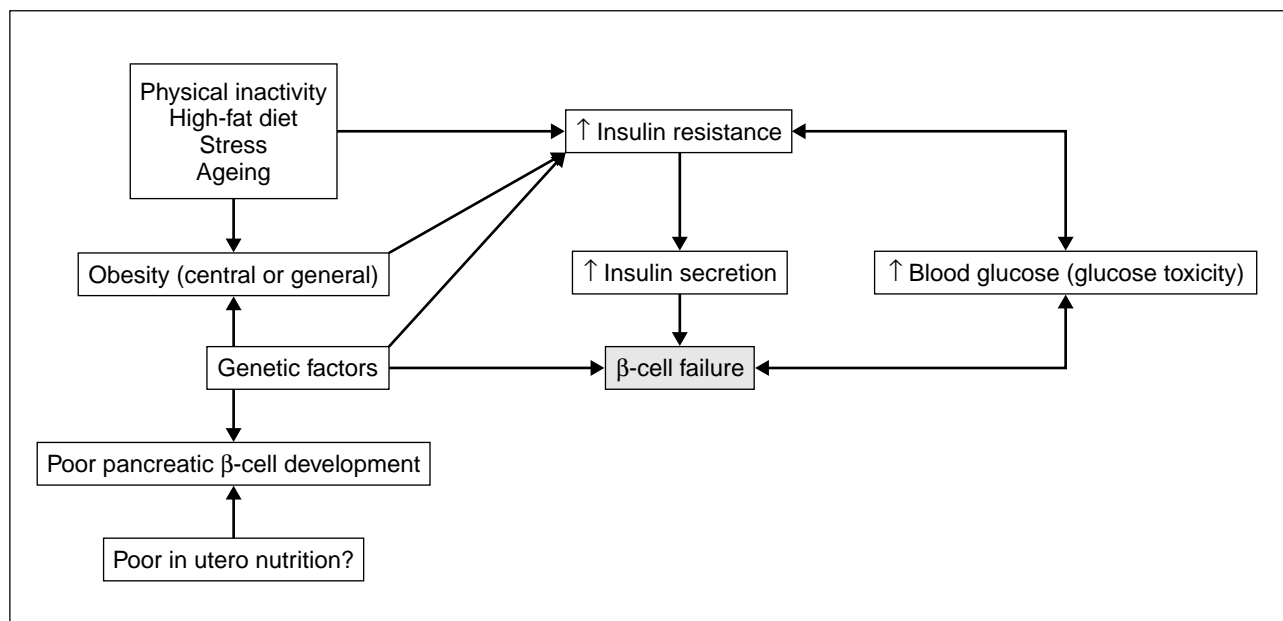
Fig 3. Pathogenesis of type 2 diabetes mellitus

formed more amyloid-like fibrils in the pancreas than did the wild-type protein.[63] Furthermore, the administration of an amylin-blocking agent (amylin 8-37) increases insulin sensitivity and alters fatty acid metabolism in rats.[64] These recent findings have created further interest in the possible pathogenic role of amylin.

Late-onset type 2 diabetes mellitus

Type 2 diabetes mellitus is a heterogeneous disease caused by interactions of multiple environmental factors as well as genetic predisposition in various populations.[3,5,8] Except in the monogenic form of diabetes, typical late-onset diabetes involves complex genetic components, which are likely to include a few main genes and other contributing genetic factors.[65] Even within the same ethnic population, the major contributing genes may vary between different individuals.

There are now numerous ongoing genome search programmes that are trying to identify susceptibility genes in different populations. Two loci, *NIDDM1* and *NIDDM2*, have been shown to be the major susceptibility loci in Mexican-American and Finnish populations, respectively.[66,67] These results, however, have so far not been reproduced in other ethnic groups. On the other hand, the candidate gene approach, which tests for the association between a particular gene variant and diabetes, has failed to identify any major genes. These candidate genes are often neither essential nor sufficient to produce type 2 diabetes on their own.[68] Some studies have suggested that polymorphisms or mutations in the transcription factors might be associated with a mild defect in insulin secretion and might be linked to late-onset type 2 diabetes.[69] But linkage analysis has excluded the *MODY* gene as the major cause of late-onset type 2 diabetes.

Conclusion

Large epidemiological studies in several populations have now confirmed that the major risk factors for type 2 diabetes include obesity and physical inactivity, as well as factors such as low birthweight. The higher risk of type 2 diabetes in relatives indicates that some individuals have an inherited susceptibility to the development of the disease. The pathogenesis of type 2 diabetes may vary among populations; in obese individuals, insulin resistance may play a predominant role in the development of impaired glucose tolerance. Decompensation from impaired glucose tolerance to overt type 2 diabetes is accompanied by and is due to impaired β-cell function. In less obese populations, primary β-cell dysfunction may play a predominant role in the pathogenesis of the disease (Fig 3).

Considerable efforts have recently been made to investigate the genetic basis of type 2 diabetes. Whole-genome studies indicate that genetic linkage to diabetes or glucose intolerance can be found in different genetic loci in different populations. Furthermore, genetic determinants of insulin deficiency and insulin resistance have been identified in a few populations.[70] Nevertheless, there is currently little consensus about the loci or identity of specific genes that confer genetic susceptibility to the development of type 2 diabetes in different populations.

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