

# Aetiology and pathology of type 2 diabetes mellitus

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The first part of our special feature this month discusses the causes and pathology of type 2 diabetes mellitus

**D**abetes mellitus (DM) is a group of metabolic disorders characterised by raised blood sugar due to defects in insulin secretion, action or both. The chronic hyperglycaemia of DM is associated with long-term damage, dysfunction and failure of organs, such as the eyes, kidneys, nerves, blood vessels and heart. The first organised

attempt to develop diagnostic criteria was probably carried out by the National Diabetes Data Group in 1979.<sup>1</sup> Later, in 1985, the diagnostic criteria were modified by the World Health Organisation (WHO).<sup>2</sup> These criteria were followed until the recent modification recommended by an expert committee (Panel 1).<sup>3</sup>

## CLASSIFICATION

The vast majority of DM cases fall into two broad aetiopathogenetic categories (Panel 2).

In the first category (type 1), the cause is the destruction of the islet cells of the pancreas due to the development of autoimmunity to these cells (Figure 1). Individuals at increased risk of developing this type of diabetes can often be identified by serological tests and genetic markers. In the second category (type 2), the cause is a combination of resistance to insulin action and an inadequately compensated insulin secretory response (Figure 2). In type 1 DM, affected persons are dependent on insulin for prevention of ketosis, coma and death (hence the other name, insulin dependent

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## Panel 1 : Diagnostic criteria

- Symptoms of diabetes (polyuria, polydipsia, unexplained weight loss) plus: random venous plasma glucose level of 11.1mmol/L or fasting plasma glucose level of 7mmol/L or two-hour plasma glucose level (after 75g glucose in oral glucose tolerance test [OGTT]) of 11.1mmol/L
- If no symptoms are present, at least two glucose tests on different days within diabetic range

## Panel 2 : Classification of diabetes mellitus

- Type 1 diabetes
- Type 2 diabetes
- Other types:
  - Diseases of the pancreas
  - Endocrinopathies
  - Drug or chemical induced
  - Other rare syndromes
  - Gestational diabetes

diabetes mellitus). On the other hand, people with type 2 DM may require insulin at a later stage for controlling hyperglycaemia, but they are not dependent on insulin for survival. That is why the condition was previously known as non-insulin dependent diabetes mellitus. The acute metabolic decompensation in type 1 DM is diabetic ketoacidosis as opposed to the non-ketotic hyperosmolar state in type 2 DM. Exceptions to this observation have been well-documented.<sup>4,5</sup> It is important to recognise which type of diabetes the patient is suffering from (Panel 3) because management is so different.

Impaired glucose tolerance (IGT) is defined as a blood glucose level higher than normal but less than that required for diagnosis of DM. This was previously called borderline diabetes, latent diabetes, chemical diabetes or pre-diabetes. It is likely that all patients with DM progress through the stage of IGT. As expected, it is of short duration in type 1 DM (as the pathogenetic process is acute) while it is of longer duration in type 2 DM. Patients are asymptomatic at this stage, so IGT is only diagnosed from blood tests.

Glucose intolerance that develops during pregnancy or is detected for the first time during pregnancy is defined as gestational diabetes mellitus (GDM).

Understandably, any pancreatic disease can give rise to secondary diabetes. However, unless and until 90 per cent of the islet cells are affected, hyperglycaemia does not ensue. Diabetes can be due to various endocrine diseases such as acromegaly or Cushing's syndrome. Hyperglycaemia can be associated with rare genetic syndromes, such as

Down's syndrome, Turner's syndrome and Klinefelter's syndrome.

The commonly used drugs responsible for hyperglycaemia are pentamidine, glucocorticoids, nicotinic acid, thyroid hormones, diazoxide, beta agonists, thiazide diuretics, phenytoin and alpha interferon. These agents are well known to precipitate diabetes in genetically susceptible individuals.

### TYPE 2 DIABETES MELLITUS

Type 2 DM is a prototypal chronic disease. It is common, serious, treatable, underdiagnosed and undertreated. The following are the main challenges associated with type 2 DM:

- Early diagnosis
- Reduction of personal and economic burden
- Improvement and sustainment of glycaemic control to prevent the development of complications and to delay progression of the disease

Vulnerability to type 2 DM is inherited, but its overt appearance is affected by medical, social and behavioural factors.

It develops gradually over decades with a long pre-diagnostic interval of mild to moderate, and sometimes, intermittent, hyperglycaemia.

### EPIDEMIOLOGY

Diabetes has reached epidemic proportions in many developing and newly industrialised nations. In 1995, an estimated

118 million people worldwide were affected with type 2 DM and, by 2010, the projected diabetic population is expected to be over 220 million (Figure 3).<sup>6</sup>

It is estimated that around 2.4 per cent of the adult population in the UK have been diagnosed with DM, and that about 80 per cent of these have type 2 DM (750,000 in England and 50,000 in Wales).<sup>7</sup> The incidence has been estimated at 1.7 cases per 1,000 population each year (85,000 per annum [pa] in England and 5,000 pa in Wales).

### RISK FACTORS

The overall pattern of type 2 DM in the population indicates that it is the result of an interaction between genetic and environmental factors.

It is important, however, to determine the extent to which individuals or a subset of the population can be identified who are at risk of developing the disease, and the nature of the host and environmental factors that convert subjects who are genetically susceptible into persons who manifest the disease.

**Host factors** A number of risk factors have been identified which make susceptible individuals succumb to the disease.

**Genetic factors** For more than 400 years, type 2 DM has been recognised as showing familial aggregation.

In contrast to type 1 DM, 38 per cent of the siblings and 33 per cent of the offspring

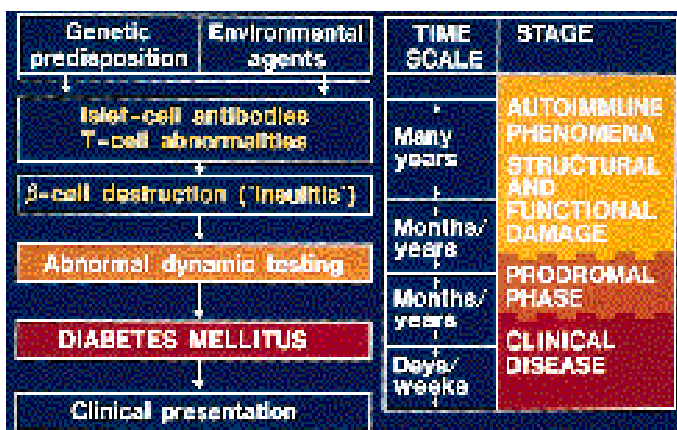


Figure 1: Chart showing the possible aetiology of type 1 diabetes mellitus

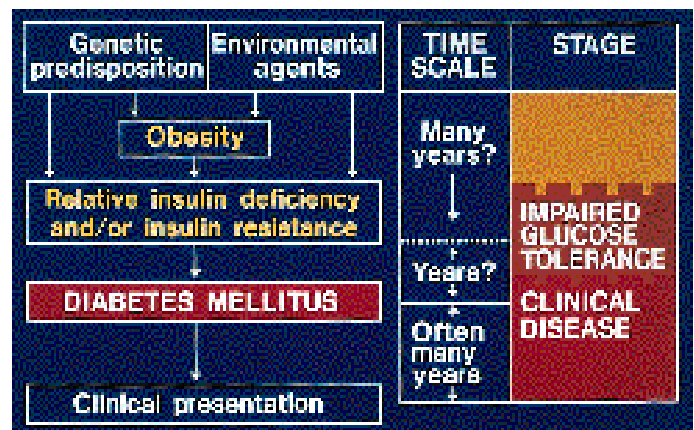


Figure 2: Possible aetiology of type 2 diabetes mellitus

### Panel 3 : Differences between types 1 and 2 diabetes mellitus

#### Type 1 DM

Young age  
Acute, static  
Ketosis prone  
Family history 10 per cent  
Insulin treatment mandatory  
Usually lean

#### Type 2 DM

Older age  
Chronic, progressive  
Ketosis resistant  
Family history > 30 per cent  
Insulin treatment optional  
Usually obese

of macrovascular disease by insulin acting like growth factors, worsening hypertension, raised very low density lipoprotein (VLDL) production from the liver, etc. This is also known as CHAOS, for:

- Coronary artery disease
- Hypertension, hyperlipidaemia
- Adult onset diabetes mellitus
- Obesity
- Stroke

of people with type 2 DM have diabetes or IGT.

The most compelling evidence of the importance of genetic determinants comes from studies of twins. The concordance rate of DM in identical twins is nearly 100 per cent in type 2 DM in comparison to 50 per cent or less in type 1.<sup>8</sup> Maturity-onset diabetes of the young, one particular form of type 2 DM, is inherited dominantly. Other than rare subgroups, human leucocyte antigen (HLA) association has not been identified. However, several mutations have been identified in cases of type 2 DM in different stages of insulin formation, secretion and action.

**Ethnic background** The prevalence and incidence of type 2 DM vary in different ethnic groups. Americans of Indian, Japanese and Mexican origin have higher rates of DM than the general population. In the UK, Britons of Asian origin have a greater prevalence of type 2 DM than those residing in India.<sup>9</sup>

**Gender** There is a greater prevalence and incidence of type 2 DM in females than in males in the US. On the other hand, in England it is believed there is a slight male excess, and in some countries, for example, India, there is a considerable male excess.

**Age** In Europe and America, the incidence of type 2 DM increases with age. The improvement in the health care and ageing of the population has meant that, in general, the prevalence of type 2 DM in the elderly is becoming greater. Also, because both insulin secretion and action generally decline with age, people born with the genetic pattern of type 2 DM display the phenotype gradually over decades.

**Glucose tolerance** Glucose tolerance is an important predictive factor for future development of diabetes. People with IGT are the ideal candidates for intervention to prevent progression to diabetes. This will be discussed further below.

**Insulin resistance or lack** Type 2 diabetes is characterised by both impaired insulin secretion and action. Genetic factors underlie both abnormalities.<sup>10,11,12</sup> Similar problems have been recognised in relatives of patients

with type 2 diabetes and women with GDM. The genetic and molecular mechanisms underlying the reduced responsiveness to insulin in the muscle, adipose tissue and liver are not completely clear, although research is in progress.<sup>13</sup> Changes in physical activity and access to rich foods are strongly related to cultural influences, but the other factors are affected by inheritance.

At the onset, one of the two abnormalities (insulin resistance and insulin lack) is usually predominant, while 10 to 15 years down the line, both abnormalities are present and prominent. In some people, fasting hyperglycaemia is the main feature, and it results from impaired basal insulin secretion.<sup>14</sup> For another group, post-prandial hyperglycaemia is the predominant abnormality, and this results from an inability to suppress hepatic glucose output after a meal. The problem here is quantitative deficiency of the insulin response to glucose, amino acid and gut hormones. Both fasting and post-prandial abnormalities are made worse by the impairment of the action of insulin on muscle and adipose tissue.

Type 2 diabetes has long been recognised as being associated with a cluster of disorders, including obesity, hypertension, dyslipidaemia and atherosclerotic heart disease. The name syndrome X, or insulin resistance syndrome, has been used to identify this pathological entity.<sup>15,16</sup> The basic problem has been recognised as hyperinsulinaemia and insulin resistance, which has several adverse effects, including aggravation

It is worth remembering that hyperinsulinaemia worsens insulin resistance by downregulating the insulin receptors.

**Obesity** An association between obesity and type 2 DM has long been recognised. While type 2 DM is frequently associated with obesity, many people who are obese (including those who are morbidly so), have completely normal glucose tolerance. Hence, obesity can be considered a precipitant of type 2 DM. The risk of developing DM varies according to the degree of obesity and age. Extensive studies have been carried out in the Pima Indians.<sup>17</sup> Obese people who had other risk factors for developing DM (eg, family history, previous gestational diabetes) manifest the disease at an earlier age than expected. On the other hand, if they are not obese, the disease may appear at a later age or may never become manifest.

**Pregnancy** Pregnancy has a major impact on carbohydrate tolerance. The increased concentration of the "anti-insulin" hormones from the placenta, particularly towards the end of the pregnancy, can result in the development of glucose intolerance. Usually within six weeks of the delivery, glucose tolerance becomes normal. However, in some cases the condition continues as type 2 DM. It is important to remember that even when glucose tolerance returns to normal after delivery, the chance of development of type 2 DM in future is higher in comparison to the general population.

**Effect of intra-uterine condition** Intra-uterine development can influence the risk of developing type 2 DM among the offspring. Foetal malnutrition is being considered an important risk factor for the future development of diabetes.<sup>18</sup>

**Dietary and other factors** For a long time, it has been known that intake of refined carbohydrate and fatty foods, a sedentary

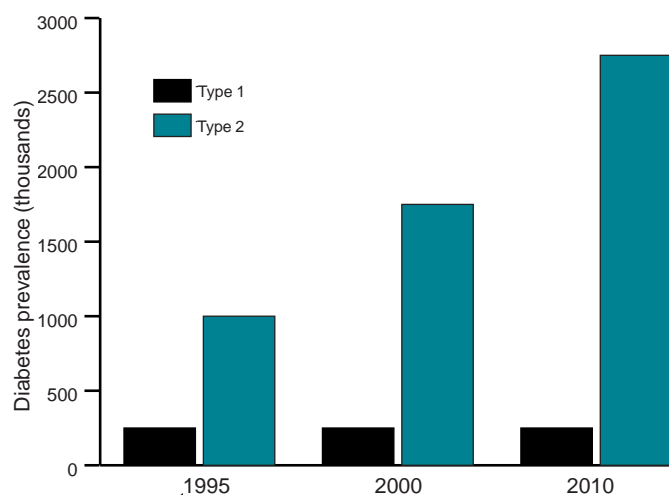


Figure 3: Projected prevalence of diabetes mellitus by 2010

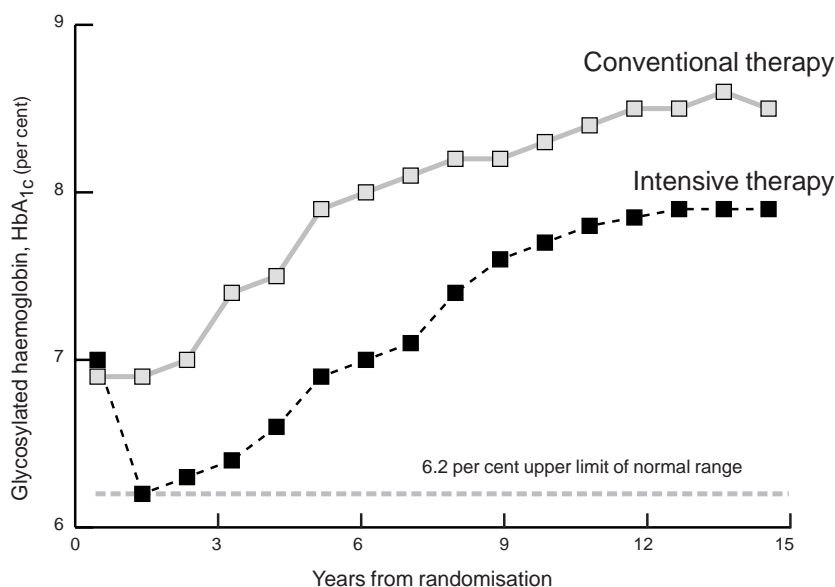


Figure 4: UKPDS showing the progressive nature of type 2 diabetes mellitus

lifestyle and higher socioeconomic status are associated with increased incidence of diabetes. Some drugs (for example, glucocorticoids), are well known for impairing glucose tolerance but they usually unmask the hyperglycaemia in the individuals concerned rather than causing diabetes.

**Environmental factors** Many studies have documented a higher prevalence of type 2 DM in urban areas than in rural areas in the developing countries. Possible reasons are more manual work and less income in the rural areas compared with the refined carbohydrate diet and sedentary lifestyle in the urban population.

*Thrifty gene hypothesis* In 1962, Neel proposed the “thrifty genotype” hypothesis as a possible explanation for the high prevalence of the disease in modern times.<sup>19</sup> According to this hypothesis, a population exposed to alternate periods of “feast” and “fast” (as was the case probably throughout most of the human evolution), has a gene, the thrifty gene, which allowed that population to survive during the period of paucity of food supply (such as during famine). Obviously, there is no proof for this hypothesis, but at least conceptually it appears valid and may provide an explanation of the secular changes in the frequency of the disease, especially in a population whose way of life has changed dramatically.

It is attractive to propose that insulin resistance may represent the thrifty gene and that when food is readily available, obesity and type 2 DM develop in those who are carriers of this gene.

*Malnutrition-related diabetes* The WHO 1985 classification (referred to at the beginning of this article) included malnutrition-related diabetes mellitus (MRDM) as a distinct class of diabetes different from other types.<sup>2</sup> MRDM occurs probably exclusively in the tropical developing countries. At least in some cases, it has been associated with consumption of the cassava root, which contains several cyanogenic glycosides. It is now classified as secondary diabetes due to pancreatic disorders.

**PROGRESS**

Type 2 diabetes is a progressive disorder in comparison with type 1 diabetes, in which immunological destruction of the islet cells causes an acute total or near-total lack of insulin. In contrast, type 2 diabetes not only emerges gradually but also tends to become more severe and difficult to treat.

This particular dimension has become much clearer since the United Kingdom Prospective Diabetes Study (UKPDS).<sup>20</sup> Also, it is clear from the study that whatever effort you put into controlling the disease, it will worsen with time (Figure 4).

We now seriously condemn the label “mild” diabetes for type 2 DM as, on the one hand, mortality is higher in the so-called “mild” diabetics in comparison with the general population and, on the other hand, glycaemic control is certainly going to worsen with time. Also, using the word “mild” will almost certainly lead to reluctance on the part of the patient to adhere to a healthy lifestyle, sensible eating and regular follow-up.

**PREVENTION**

One of the pioneers in the field of diabetes was E. P. Joslin. He was quoted as saying in 1921, “... it is proper at the present time to devote time not alone to treatment, but still more, as in the case of typhoid fever, to prevention. The results may not be quite so striking or as immediate, but they are sure to come and important.”

The natural history and pathophysiology of type 2 diabetes offer an opportunity for prevention. This can be done in two ways: population approach and target approach. A population approach is certainly very important but at the same time is very difficult. The main issue is to make the whole population aware of why DM is a killer disease. The actions needed include a healthy lifestyle, regular exercise and attempts to prevent obesity.

In the target approach, the first step for prevention is to identify people at risk of developing type 2 diabetes (see above). People who develop type 2 DM pass through a stage of IGT, the duration of which varies depending on several factors. The prevalence of IGT varies widely in the general population from as low as 1 per cent to as high as 15 per cent.<sup>21</sup> Again, rates of progression of IGT to overt diabetes vary in different populations from as high as 8.6 per cent per year in Pima Indians to as low as 1.8 per cent per year in the Danish population.<sup>21</sup> However, prospective studies have demonstrated that IGT may revert to normal glucose tolerance.<sup>22</sup>

Lifestyle modifications such as dietary modification (avoiding Coca-Colonisation), increase in physical activity and a combination of the two are proven to be helpful in preventing progress of IGT to type 2 DM. Pharmacological intervention of IGT with sulphonylureas, metformin, acarbose or thiazolidinediones may be regarded as overmedication of a “non-disease.” On the other hand, IGT has been clearly identified to be associated with increased morbidity and mortality when compared with the general population. To answer these issues, a

diabetes prevention programme was launched in the United States of America in 1996 to test the effects of lifestyle intervention or pharmacotherapy on progression of diabetes in 4,000 subjects with IGT. Participants have been randomised into lifestyle intervention, troglitazone, metformin or placebo. The result is expected in 2002.

#### CONCLUSION

Type 2 diabetes mellitus is a heterogeneous disorder requiring both genetic and environmental factors. Hyperglycaemia in type 2 diabetes results from a combination of insulin resistance and relative (rather than absolute) insulin deficiency. An insight into the aetiopathogenesis helps to determine a better approach to the disease. It is crucial to identify the hidden cases of type 2 diabetes in the community. Diabetes UK (previously the British Diabetic Association) has recently launched a campaign to identify the missing million cases in the UK. Education for the general population, and in particular, for the patients, is the key to preventing and controlling this type of diabetes and reducing the complications arising from it.

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