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What is type 2 diabetes?

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Abstract

Type 2 diabetes is a common metabolic disorder characterized by chronic hyperglycaemia. It is associated with a reduced life expectancy owing to a greater risk of heart disease, stroke, peripheral neuropathy, renal disease, blindness and amputation. At present, the best predictors of increased diabetes risk and progression to diabetes are an elevated fasting plasma glucose, an abnormal glucose tolerance test, obesity and evidence of impaired insulin action. However, the mechanisms by which people with impaired fasting glucose and/or abnormal glucose tolerance 'progress' to overt type 2 diabetes are not completely understood. Moreover, type 2 diabetes is defined in a 'negative' sense (hyperglycaemia occurring in the absence of evidence of autoimmune destruction of islet cells). This has two consequences – one is the heterogeneity of the disease, the other is that the disease is identified purely in terms of hyperglycaemia, to a certain extent ignoring the underlying mechanisms that lead to the disease. In this review, we explore some of these mechanisms in an attempt to remind readers that hyperglycaemia is one of many abnormalities in type 2 diabetes.

Keywords

Type 2 diabetes; insulin secretion; insulin action; incretin hormones; prediabetes

Glucose: too simplistic a definition of diabetes?

Diabetes is a complex metabolic disorder characterized by chronic hyperglycaemia, which leads to microvascular and macrovascular complications. Hyperglycaemia arises because of relative or absolute insulin deficiency. Broadly speaking, diabetes can be divided into two categories – immune-mediated diabetes (type 1 diabetes) and non-immune-mediated diabetes (type 2 diabetes). In essence, such a definition characterizes type 2 diabetes as something it is not, rather than specifying a particular pathogenesis or another positive definition (1). In practice, it is sometimes difficult (and unnecessary) to differentiate between the two subtypes but the absence of a positive definition articulates the difficulty in describing type 2 diabetes simply and succinctly (2).

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The prevalence of the disease in the United States has doubled over the last two decades, in parallel with an epidemic of obesity. Of 23.6 million Americans affected, 90% have a clinical diagnosis of type 2 diabetes (3). Diabetes is diagnosed when fasting plasma glucose is greater than 7 mmol/l (126 mg/dL), or random plasma glucose exceeds 11.1 mmol/l (200 mg/dL). These diagnostic criteria were established by ADA in 1997, based on the observation that these values are strongly associated with an increased incidence of microvascular complications, such as retinopathy. Most recently, an expert committee comprising of members of American Diabetes Association (ADA), the International Diabetes Federation (IDF), and the European Association for the Study of Diabetes (EASD) recommended that a haemoglobin A_{1c} (HbA_{1c}) greater than 6.5% is included as a diagnostic criterion (4). This is because an HbA_{1c} >6.5% is also correlated with risk of diabetic retinopathy. Although this test is less affected by diurnal variation and activity, it has its own problems. HbA_{1c} is affected by quantitative and qualitative variations in haemoglobin, which accompany physiologic states such as pregnancy and disease states such as renal failure, thalassemia and other haemoglobinopathies (5). Other problems include the lack of standardization of the test and its sensitivity.

Pre-diabetes has been a term used to describe situations where there are abnormalities of glucose metabolism but the criteria for diabetes are not met. For example, a fasting plasma glucose >5.6 mmol/l (100 mg/dl) but <7.0 mmol/l (126 mg/dl) or a 2-hour glucose after oral glucose tolerance testing >7.8 mmol/l (140 mg/dl) but <11.1 mmol/l (200 mg/dl). Besides the increased risk of progression to diabetes, which rises in concert with the degree of rise in fasting and 2-hour plasma glucose (Figure 1), there is an increased risk of macrovascular disease (6). Unfortunately, both fasting and post-challenge glucose measurement is encumbered by significant variability and lack of reproducibility. Furthermore, such elevations do not guarantee progression to diabetes. This underlies the recommendation that the term 'pre-diabetes' be abandoned and replaced with Impaired Fasting Glucose (IFG) and/or Impaired Glucose Tolerance (IGT).

Pathophysiologic mechanisms underlying the transition to diabetes

The absence of a positive definition of type 2 diabetes, suggests that multiple mechanisms lead to disease. Established type 2 diabetes is characterized by defective and delayed insulin secretion as well as abnormal postprandial suppression of glucagon. These abnormalities explain in part the defective suppression of endogenous glucose production after meal ingestion and contribute to postprandial hyperglycaemia, as shown in Figure 2 (7). It is uncertain whether this results from an inherent defect in the α -cells of people with type 2 diabetes or a manifestation of decreased intra-islet insulin that suppresses α -cell secretion.

The islets of people with longstanding type 2 diabetes have a characteristic appearance with prominent amyloid deposition and a decrease in functional β cells (8). These anatomical defects underlie the decrease in insulin secretion. However, the fact that defects in insulin secretion arise early in the pathogenesis of diabetes and probably precede any of the anatomic changes described above is important. Insulin is secreted in a pulsatile manner resulting in high-frequency oscillations of insulin concentration in the portal and (to a lesser extent) the peripheral circulation. In general, stimuli of insulin secretion increase the mass and/or the frequency of such pulses (9). This pulsatility is disordered in people with type 2 diabetes as well as in glucose-intolerant first degree relatives of affected patients, implying that such abnormalities arise early in the course of disease (10). Furthermore, common genetic variation that affects β cell function and therefore insulin secretion in quantifiable ways increases the risk of progression from glucose intolerance to type 2 diabetes (11).

Another important abnormality observed in type 2 diabetes is an impaired ability of insulin to stimulate glucose uptake and suppress glucose release. Such defects in insulin action (colloquially referred to as insulin resistance) also arise early in the course of disease development and contribute to its pathogenesis. Indeed, when insulin secretion is expressed as a function of the prevailing insulin action, across the spectrum of IFG and IGT, it is clear that parallel defects in secretion and action underpin the progression to type 2 diabetes (12). Intriguingly, genome-wide association studies seeking to identify genetic loci associated with predisposition to disease (and therefore implicate biological pathways important in the pathogenesis of diabetes) have suggested that the majority of such loci affect β -cell function and not insulin signaling. Moreover there are several loci that modulate fasting and post-challenge glucose concentrations independent of diabetes risk (13). Another important parameter is glucose effectiveness – the ability of glucose *per se* to stimulate its own uptake and suppress its own release (14; 15). A multitude of mechanisms has been invoked in the pathogenesis of impaired insulin action and glucose effectiveness, including impairment of insulin signalling by pro-inflammatory cytokines and adipokines, but a unifying mechanism remains elusive.

Diminished insulin action in adipocytes results in increased lipolysis and high concentrations of free fatty acids (FFAs). There is evidence that an increase in FFAs leads β cell impairment, stimulates hepatic gluconeogenesis and adversely affects glucose effectiveness (16). Lower concentrations of incretins such as GLP-1 and GIP, produced in the small intestine, have been observed in people with type 2 diabetes (17). There have also been reports of abnormal incretin concentrations in people with impaired fasting glucose and impaired glucose tolerance, implying that incretin deficiency may play a role in the pathogenesis of diabetes (18). However, there is a lack of consistent evidence to support this.

It is also important to appreciate that despite intervention (pharmacologic as well as lifestyle modification), glucose concentrations increase over time in people with type 2 diabetes presumably due to a decline in insulin secretory capacity requiring additional intervention over time (19; 20). Indeed the ADOPT (A Diabetes Outcome Progression Trial) demonstrated that there is an appreciable rate of monotherapy failure over a 4-year period – likely due to progression of disease (21).

Can diabetes resolve?

Once the diagnosis of type 2 diabetes has been established, in the absence of contributing factors, is there any hope of a remission? From a glycaemic standpoint it is certainly possible, but it remains to be ascertained whether such aggressive intervention significantly alters the underlying pathophysiology of the disease or merely arrests it. The effectiveness of aggressive lifestyle modification in preventing progression to diabetes in a high-risk group was clearly established by the Diabetes Prevention Program (DPP), where a 7% weight loss as result of a combination of caloric restriction and exercise led to a 58% reduction in the incidence of diabetes after 3 years (22). In addition, weight loss achieved by lifestyle intervention after the diagnosis of diabetes seems to produce the same results: a small study that included 41 patients with early-stage type 2 diabetes demonstrated a 52% remission rate after a modest 3.7% weight loss at 6 years (23). More remission rate data will be available in the next few years with the completion of a large-scale 12-year Look AHEAD (Action for Health in Diabetes) trial, designed to examine the effects of aggressive lifestyle intervention in over 5000 obese patients with type 2 diabetes (24). Compared to the DPP trial, the Look AHEAD trial targets a greater weight loss of 10% and greater caloric restriction. The interim analysis at 1 year showed that an 8.6% weight loss in the intensive intervention group was paralleled by a 14.7% decline in the percentage of patients meeting

the criteria for metabolic syndrome. The specific remission rates for diabetes were not reported (25).

The use of oral agents, such as acarbose, metformin or thiazolidinediones, in people without type 2 diabetes has also led to the suggestion that early pharmacotherapy might prevent diabetes and induce remission. However, discontinuation of pharmacotherapy is not necessarily associated with a sustained improvement in glycaemia. Thiazolidinedione treatment in women with a history of gestational diabetes, decreases the annual incidence of type 2 diabetes (at least compared to the expected rate) (26). Indeed in the Troglitazone in Prevention of Diabetes (TRIPOD) study, beneficial effects of intervention on insulin secretion and action persisted 8 months after discontinuation of treatment (27). There is some evidence that intensive insulinization by means of continuous subcutaneous insulin infusion soon after the diagnosis of type 2 diabetes can lead to substantial improvement in the glucose profile, with some patients demonstrating near-normal glycaemic patterns on fasting blood glucose and HbA_{1c} measurements and an intravenous glucose tolerance test at 1 year (28). This is similar to the observations made in ketosis-prone type 2 diabetes, more commonly seen among African-Americans and other ethnic minorities, where 42% remission rates at 20 months have been reported (29).

Bariatric surgery leads to a remission of type 2 diabetes in 40–90% of the cases depending on the procedure undertaken (30). In fact, given the difficulties of achieving and maintaining weight loss with lifestyle modifications alone, bariatric surgery has been proposed as a 'cure' for diabetes. Interestingly, a dramatic improvement in the glucose profile and even a remission of diabetes may occur within the first days after the procedure, before any weight loss ensues. Resolution of diabetes is more common with malabsorptive procedures, and bears some relationship to the length of gut excluded by the procedure. Multiple mechanisms have been proposed to explain this phenomenon, but there have been few systematic studies. It has been suggested that an interruption of the entero-insular axis by way of alteration of incretin concentration plays a central role, but confirmatory studies are largely lacking. Alternatively caloric restriction may directly improve insulin action and suppress hepatic gluconeogenesis. Moreover, the effect of surgery on the defects in insulin secretion (e.g. pulsatility and islet function) is unknown.

Drugs and disease associated with diabetes

Numerous medications, some of which are listed in Table 1, can worsen glucose metabolism and precipitate diabetes. The odds ratio for developing diabetes while taking glucocorticoid therapy ranges 1.3–2.3 (31) and is dose-dependent. The hyperglycaemia is more severe in the post-prandial period and is related to a reduction in insulin sensitivity (32). Since inflammation is the salient feature of the medical conditions for which corticosteroids are generally prescribed and systemic inflammation is recognized as a risk factor for developing impaired insulin action, it may be that patients who require corticosteroid therapy already have an underlying predisposition to developing diabetes.

There has been much debate about whether the higher prevalence of diabetes in people affected by schizophrenia reflects an increased risk embedded in this psychiatric disease *per se*, the associated lifestyle and family risk factors, or the adverse metabolic effects of antipsychotic medications. Data from pharmacoepidemiologic studies suggest that there is an increased risk of diabetes with olanzapine and clozapine compared to typical antipsychotics or other atypical agents such as aripiprazole or risperidone (33). Weight gain related to the use of these agents probably accounts for the majority of cases of new-onset diabetes occurring during treatment. However, there may be a substantial proportion of patients in whom rapid, dramatic development of hyperglycaemia occurs independent of

adiposity, probably reflecting direct impairment of β cell function by the antipsychotic drug. It has been proposed that this effect may be mediated by antagonistic actions on the M_2 muscarinic receptors in the pancreas (34).

The incidence of new-onset diabetes after solid organ transplantation is increasing and is linked most closely to immunosuppressive therapy with corticosteroids, calcineurin inhibitors and sirolimus (35). Weight gain is a common predisposing factor, but there is evidence of direct islet cell toxicity from calcineurin inhibitors. Animal studies, as well as in-vitro studies of human pancreatic islets, have demonstrated decreased beta cell volume, insulin content and insulin release with ciclosporin treatment (36; 37). Tacrolimus and sirolimus may be even more diabetogenic than ciclosporin, with some studies showing 70% higher incidence of diabetes in the two years after a kidney transplant, compared to non-tacrolimus based immunosuppression (38).

Protease inhibitors, widely used to treat HIV infection, are associated with the development of impaired glucose tolerance or type 2 diabetes. In vitro studies suggest that these drugs impair the insulin-stimulated glucose uptake in skeletal muscle and adipocytes. Studies of HIV-infected patients who had normal glucose tolerance before the initiation of therapy revealed impaired suppression of lipolysis and impaired β cell function (39).

Uncommon endocrine conditions such as acromegaly, Cushing's syndrome, pheochromocytoma and glucagonoma can precipitate type 2 DM or unmask an underlying predisposition to it. The prevalence of diabetes mellitus and that of IGT in acromegaly is reported to be in the range 16–56%. GH has physiological effects on glucose metabolism, stimulating gluconeogenesis and lipolysis, which results in increased plasma glucose and FFA concentrations (40). In Cushing's syndrome the prevalence of diabetes varies between 20–50% (40), but this prevalence is probably underestimated because in the presence of a normal fasting glucose, oral glucose tolerance testing is not routinely performed. With pheochromocytoma, there is an impaired insulin secretion possibly via overstimulation of the adrenergic receptors on the pancreatic islets. There are multiple case reports of postoperative hypoglycaemia occurring after surgical removal of the tumor, which may be due to rebound hypersecretion of insulin as catecholamines fall precipitously (41; 42). Hypersecretion of glucagon from α cell tumors results in diabetes in 80–90% of cases.

Conclusion

Type 2 diabetes is a heterogeneous disorder where a multidimensional metabolic dysregulation leads to hyperglycaemia. Various medications and endocrine conditions may be associated with the onset of diabetes. Aggressive measures such as lifestyle intervention, early intensive pharmacotherapy and bariatric surgery can re-establish euglycaemia, but it is unclear if the underlying pathophysiological changes are actually reversed.

What's New?

- Type 2 diabetes is a heterogeneous disorder characterized by impaired insulin secretion and insulin action that lead to hyperglycaemia
- Impaired glucose effectiveness and inadequate post-prandial glucagon suppression contribute significantly to hyperglycaemia
- Elevated free fatty acids and altered incretin hormone concentrations exacerbate the metabolic abnormalities in diabetes and may be implicated in pathogenesis, although consistent evidence is lacking

- Medications such as corticosteroids, calcineurin inhibitors, protease inhibitors and atypical antipsychotics are associated with the onset of diabetes
- Aggressive measures such as lifestyle intervention, early intensive pharmacotherapy and bariatric surgery can re-establish euglycaemia, but it is unclear if the underlying pathophysiological changes are actually reversed

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Figure 1. Cumulative incidence of diabetes according to initial fasting plasma glucose
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Diabet Car 1998; **21**: 1408–13.

Figure 2.

a. Plasma glucose concentrations observed on glucagon-suppressed vs. non-suppressed study days

b. By design, insulin concentrations did not differ on both days of the experiment. However, on one day, glucagon concentrations were suppressed to mimic the postprandial suppression of glucagon seen in non-diabetic individuals

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Table 1**Drugs that worsen diabetes**

Antiviral therapy	Interferon
	Protease inhibitors
Immunosuppressants	Corticosteroids
	Ciclosporin
	Tacrolimus
	Sirolimus
Atypical antipsychotics	Clozapine
	Risperidone
	Olanzapine
Others	Niacin
	Pentamidine
	β -blockers
	Thiazides