Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future

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Glucose metabolism is normally regulated by a feedback loop including islet β cells and insulin-sensitive tissues, in which tissue sensitivity to insulin affects magnitude of β-cell response. If insulin resistance is present, β cells maintain normal glucose tolerance by increasing insulin output. Only when β cells cannot release sufficient insulin in the presence of insulin resistance do glucose concentrations rise. Although β-cell dysfunction has a clear genetic component, environmental changes play an essential part. Modern research approaches have helped to establish the important role that hexoses, aminoacids, and fatty acids have in insulin resistance and β-cell dysfunction, and the potential role of changes in the microbiome. Several new approaches for treatment have been developed, but more effective therapies to slow progressive loss of β-cell function are needed. Recent findings from clinical trials provide important information about methods to prevent and treat type 2 diabetes and some of the adverse effects of these interventions. However, additional long-term studies of drugs and bariatric surgery are needed to identify new ways to prevent and treat type 2 diabetes and thereby reduce the harmful effects of this disease.

The epidemic of type 2 diabetes

The worldwide explosion of obesity has resulted in an ever-increasing prevalence of type 2 diabetes—a non-communicable disease that affects more than 370 million people. Without concerted efforts to address the pathogenesis and treatment of this syndrome, the harmful macrovascular and microvascular outcomes of type 2 diabetes will remain a major burden for decades to come. In this Review we examine aspects of the pathogenesis and treatment of type 2 diabetes, and discuss future needs if the most damaging result of obesity is to be reversed.

Pathogenesis of type 2 diabetes: from the past to the present and future

The past: identification of β-cell dysfunction and insulin resistance

Development of the insulin radioimmunoassay led to the finding that patients with early-maturity-onset diabetes produced insulin and secreted this hormone in response to nutrient ingestion. Subsequently, defects in the ability of islet β cells to respond to intravenous secretagogues (including glucose) were reported in these patients. Additionally, these patients did not respond well to insulin, and were thus deemed to be insulin insensitive. This insulin insensitivity was shown to contribute to increased production of glucose by the liver and decreased uptake of glucose in muscle and adipose tissue. Nowadays, some of these abnormalities are attributed to adiposity, especially adiposity within the intra-abdominal cavity.

The present: the crucial role of β cells to glucose homoeostasis by feedback regulation

The importance of insulin resistance and β-cell dysfunction to the pathogenesis of type 2 diabetes was debated for a long time; many thought that insulin resistance was the main abnormality in type 2 diabetes, and that inability to secrete insulin was a late manifestation. This notion changed with the finding that, as with most endocrine systems in human beings, a feedback loop operates to ensure integration of glucose homoeostasis and maintenance of glucose concentration in a narrow range.

This feedback loop relies on crosstalk between β cells and insulin-sensitive tissues (figure 1). Insulin released in response to β-cell stimulation mediates uptake of glucose, aminoacids, and fatty acids by insulin-sensitive tissues. In turn, these tissues feed back information to islet cells about their need for insulin. The mediator of this process has not been identified, but probably includes integration between the brain and humoral system. If insulin resistance is present, as often happens in people with obesity, β cells increase insulin output to maintain normal glucose tolerance. However, if β cells are incapable of this task, plasma concentrations of glucose increase.

Although the distinction between impaired fasting glucose and impaired glucose tolerance (sometimes referred to as prediabetes) and diabetes is established by testing of 2 h glucose concentrations after fasting and a standardised load of oral glucose, these disturbances form a continuum in which the magnitude of reduction in β-cell function establishes the degree of increase in plasma glucose. Insulin resistance is already well established if impaired glucose tolerance is present;
rises in glucose concentrations, even within the normal range, are due to a continuous fall in β-cell function.\textsuperscript{9} Further progressive deterioration of β-cell function accounts for the evolving natural history of the disease, from impaired glucose tolerance to type 2 diabetes.\textsuperscript{9,10,11}

Reduced β-cell function is already present in groups at increased risk of diabetes (eg, first-degree relatives of patients with diabetes,\textsuperscript{12} women with gestational diabetes\textsuperscript{13} or polycystic ovary syndrome,\textsuperscript{14} and elderly people\textsuperscript{15}) and underlies progression to the disease. Furthermore, β-cell function is heritable\textsuperscript{16} and is crucially important to differences in glucose intolerance and rates of type 2 diabetes between various racial and ethnic groups.\textsuperscript{17}

Despite advances in understanding of the importance of insulin resistance and β-cell dysfunction to the pathogenesis of type 2 diabetes and high-risk states, the disease process is clearly heterogeneous, and includes other pathogenic factors.

Genes, environment, and development of type 2 diabetes

Genes and the environment together are important determinants of insulin resistance and β-cell dysfunction (figure 2). Because changes in the gene pool cannot account for the rapid increase in prevalence of type 2 diabetes in recent decades, environmental changes are essential to understanding of the epidemic.

Advances in technology and analytical approaches have identified genes linked with type 2 diabetes. With use of candidate-gene approaches, \textit{PPARG} was the first gene identified.\textsuperscript{18} Subsequently, mostly with use of genome-wide association studies, more than 50 gene loci have been linked with type 2 diabetes.\textsuperscript{19} Furthermore, 53 loci have been linked with concentrations of insulin and glucose (however, not always with both fasting and 2 h concentrations of glucose), of which 33 are also associated with type 2 diabetes.\textsuperscript{19,20} Although some loci are associated with obesity and insulin resistance, most are linked with β-cell function.\textsuperscript{21} Gene products for most of these loci have not been definitively identified. Together, these genes do not explain much of the genetic basis of type 2 diabetes; the use of genotype risk scores only slightly improves prediction of subsequent diabetes compared with more frequently used clinical risk factors.\textsuperscript{22,23}

Aside from obvious increases in caloric intake and decreased energy expenditure, other environmental factors seem to be important. Nutrient composition, specifically increased amounts of dietary fat (particularly saturated fat), are important to development of obesity, insulin resistance, β-cell dysfunction, and glucose intolerance.\textsuperscript{24} Furthermore, an ageing-associated reduction in the responsiveness of β cells to carbohydrate partly underlies the fall in glucose tolerance with ageing.\textsuperscript{25} The in-utero environment, established partly by the mother’s body size, could produce epigenetic and gene-expression changes that affect the risk of development of obesity and type 2 diabetes for the offspring.\textsuperscript{26} Recent

Figure 1: Feedback loop between islet β cells and insulin-sensitive tissues
(A) Insulin interacts in the liver to suppress glucose production, and in muscle and adipose tissue to stimulate uptake of glucose, aminoacids, and fatty acids. The amount of insulin released to maintain normal glucose homoeostasis is established by prevailing insulin sensitivity. This feedback is probably mediated through neuronal and humoral mechanisms, but exact mediators are still not known. (B) When insulin resistance develops in insulin-sensitive tissues, feedback to β cells ensures that the cells increase insulin output to maintain normal glucose tolerance. (C) When β cells are incapable of increasing insulin output in the presence of insulin resistance, the result is development of increased glucose concentrations, which initially manifests as impaired glucose tolerance. Because β-cell dysfunction progresses, further elevations in glycaemia occur and diabetes is the eventual result.
discussion has also focused on the role of environmental chemicals in the epidemics of obesity and diabetes.\textsuperscript{27}

**Further delineation of the roles of reduced β-cell numbers and α-cell dysfunction**

The reduction of β-cell numbers in type 2 diabetes is well known.\textsuperscript{28–31} The basis for this loss is multifactorial, and includes glucolipotoxicity\textsuperscript{32} and amyloid deposition that result in β-cell apoptosis through oxidative and endoplasmic-reticulum stress.\textsuperscript{31} This loss is not counterbalanced by replacement with new β cells, because the human pancreas seems to be incapable of renewing these cells after 30 years of age.\textsuperscript{33} Although a reduction in β-cell mass occurs in type 2 diabetes, the magnitude of this abnormality is clearly insufficient to explain the degree of impairment in insulin release. Whether the underlying defect in β-cell function is important as an initiator of β-cell loss, and whether increasing secretory demand on each individual β cell as numbers decrease causes ongoing loss of β cells, remains to be defined. Elucidation of the importance of β-cell function compared with mass could have important implications for development of approaches to preserve β cells and help to maintain or improve glucose tolerance.

Although less well studied, dysregulated release of glucagon by α cells, which manifests as increased concentrations of fasting glucagon and failure to adequately suppress glucagon release after meal ingestion, contributes to the development of hyperglycaemia.\textsuperscript{34} Whether this dysregulation is a primary change in α cells or is secondary to an abnormality in β-cell function is not yet resolved. However, islet blood flows from β cells to α cells and then to somatostatin-producing δ cells;\textsuperscript{35} high concentrations of insulin bathing α cells are capable of suppression of glucagon release.\textsuperscript{36} Other β-cell products—eg, zinc, γ-amino-butyric acid, or glutamate—might also regulate glucagon release.\textsuperscript{37} Approaches that reduce glucagon release or impair its action to raise glucose concentrations could represent additional therapeutic alternatives for type 2 diabetes.\textsuperscript{38}

**Important roles of the intestine and brain**

The gastrointestinal tract produces various peptides, not all of which directly modulate nutrient absorption. Glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), collectively known as incretins, act on the pancreatic islet. GLP-1 is more important, and acts both on β cells to enhance insulin secretion and on α cells to suppress glucagon secretion.\textsuperscript{39} Therefore, the β-cell response to GLP-1 after meal ingestion has to be deficient, as noted after intravenous administration of GLP-1 under controlled conditions.\textsuperscript{40} This deficient response is consistent with a model of global deficiency in β-cell responsiveness to many secretagogues (eg, sulfonylurea antidiabetics, aminoacids, and β-adrenoreceptor agonists).\textsuperscript{41} Although GLP-1 acts directly on α cells to suppress glucagon release, the effect of this mechanism compared with modulation by β-cell products is uncertain, both in healthy people and in those with type 2 diabetes (in which glucagon is inadequately suppressed during meals). Increased concentrations of GLP-1 have been reported after bariatric surgery, and are thought to account for many of the beneficial effects of the intervention, particularly in patients with type 2 diabetes.\textsuperscript{42} However, increased GLP-1 is not the only mechanism by which glucose lowering can occur after this surgical procedure.\textsuperscript{43}

Bile acids are also important in the regulation of glucose metabolism. They are endogenous ligands of the farnesoid X receptor, and activation of the receptor results in release of the fibroblast growth factor (FGF) 19.\textsuperscript{44} Bile acids also activate G-protein-coupled bile-acid receptor 1 located on intestinal L cells, leading to GLP-1 secretion.\textsuperscript{45} In human beings, infusion of bile acids intraduodenally in a dose-dependent manner increases plasma concentrations of FGF19, with smaller effects on concentrations of GLP-1 and cholecystokinin.\textsuperscript{46} Because FGF19 has insulin-like effects (it induces synthesis of glycogen and proteins, and inhibits glucose production)\textsuperscript{47} the biliary system might have an underappreciated role in modulation of glucose homeostasis.

The intestinal microbiome also seems to be important to the pathophysiology of type 2 diabetes.\textsuperscript{48} The microbiome has about 100 times more genetic information than has the human genome, together comprising the human metagenome. Many products of the microbiome provide functions beyond that of the host genome, thereby serving an important role in human physiology. These gut communities are thought to play an important part in several conditions and disorders (eg, obesity and type 2 diabetes), although
which bacterial species cause changes to human metabolism is not clear. Findings from two studies that used faecal samples suggested that functional changes in the gut microbiome might be directly linked to development of type 2 diabetes; however, metagenomic markers differ between populations, suggesting that their ability to predict development of diabetes will probably vary. Findings from a recent proof-of-concept study showed improvements in insulin sensitivity in patients with metabolic syndrome 6 weeks after infusion of intestinal microbiota from lean individuals. Lastly, different gut flora might affect nutrient absorption, because in human beings nutrient load can alter the faecal bacterial community in a short time.

The nervous system is another important regulator of metabolic processes. Both sympathetic and parasympathetic nervous systems control glucose metabolism, directly through neuronal input, and indirectly through the circulation to affect release of insulin and glucagon and production of hepatic glucose. In human beings, the vagus is important in regulation of islets, because severing of this nerve results in impaired insulin secretion. The hypothalamus is an important integrator, because its ablation in rats results in dysregulation of β cells and development of hyperinsulinaemia. This brain region also regulates hepatic production of glucose through the actions of insulin, glucose, and fatty acids. Insulin action at this site is also essential in regulation of bodyweight, with decreased activity leading to obesity. Inflammation-induced neuronal injury occurs rapidly in rodents fed a high-fat diet. Findings from imaging studies of obese and lean people suggest that structural changes occur in the hypothalamus, consistent with the occurrence of gliosis in obesity. Finally, clock genes expressed in the brain are important in establishment of circadian rhythmicity and, together with sleep, have become a focus of investigation because changes in diurnal patterns and quality of sleep can have important effects on metabolic processes.

Systemic and islet inflammation

Obesity is often characterised by systemic inflammation, and preclinical evidence links systemic inflammation to β-cell dysfunction. Markers of systemic inflammation, including C-reactive protein and its upstream regulator interleukin 6, are cross-sectionally associated with insulin sensitivity and β-cell function. Lifestyle change and pharmacological drugs improve markers of inflammation, and have been associated with improvements in β-cell function in patients with type 2 diabetes.

Direct effects of inflammation on β cells arise from activation of the intraislet immune response. Glucose and fatty acids increase production of interleukin 1β in islets, and naturally occurring antagonists (particularly interleukin 1 receptor antagonist) balance and regulate the action of interleukin 1β in islets and other tissues.

Circulating concentrations of interleukin 1β and interleukin 1 receptor antagonist are increased in patients with type 2 diabetes; however, lower concentrations at the time of initiation of interleukin 1 receptor antagonist treatment could predict maintenance of improved β-cell function after intervention to reduce islet inflammation.

Expansion of adipose tissue is associated with accumulation of activated macrophages that express several proinflammatory genes, including cytokines (eg, tumour necrosis factor α) that locally impair insulin signalling. A feed-forward process, in which activation of transcription factors causes further production of proinflammatory cytokines, also plays a part. When production of these cytokines is sufficient, they are released into the circulation where they can act at distant sites (eg, the liver and skeletal muscle) to worsen insulin resistance. A similar process can occur in the liver with Kupffer cells (resident macrophages) and recruited macrophages. Hypothalamic inflammation might also contribute to central leptin resistance and weight gain.

The future: genetics, epigenetics, and omics

Although understanding of the genetics of type 2 diabetes has advanced rapidly, much remains unknown. How genes interact with the environment to cause progressive loss of β-cell function is unclear. Environmental factors and hyperglycaemia could contribute to epigenetic changes in DNA and histones, thereby modifying gene expression in organs implicated in the pathogenesis and progression of type 2 diabetes, including in β cells. Whether such changes contribute to the increased risk of type 2 diabetes and the progression of disease will be of interest. Finally, because only a small proportion of the risk of type 2 diabetes can be attributed to identified genetic loci, the search for rarer variants with approaches such as exome sequencing might provide additional insights and possible therapies.

The so-called omics (eg, metabolomics, lipidomics, proteomics, genomics, and transcriptomics) are based on the study of constituents of the cell or body in a collective way. The findings made with use of these approaches are being integrated to better understand the pathophysiology of type 2 diabetes and the heterogeneity of responses to different glucose-lowering therapies. Findings from studies that used metabolomics and lipidomics showed that increases in branched-chain and aromatic aminoacids were associated with obesity and type 2 diabetes. Furthermore, patients with high concentrations of specific six-carbon sugars, aminoacids, and fatty acids, and low concentrations of other aminoacids and fatty acids, had an increased risk of developing type 2 diabetes over a 7 year follow-up. Whether all or some of these substrate markers are associated with genetic determinants, dietary factors, or the actions of gut microbes has not been established.

In the long term, these new approaches should identify additional genes and metabolic markers; profiles
The rate of introduction of new classes of drugs has accelerated during the past 20 years. Two classes (animal insulin and inhaled insulin; red) are essentially no longer available as therapeutics. (B) Different classes of drugs act on different organ systems. Insulin is a replacement for the natural product of islet β cells. Classic organ systems that have been targeted for decades comprise the pancreatic islet, liver, muscle, and adipose tissue. Non-classic targets have been focused on recently, and include the intestine, kidneys, and brain. DPP4 = dipeptidyl peptidase 4. Sulfonylurea antidiabetics, biguanide antidiabetics, α-glucosidase inhibitors, and peroxisome proliferator-activated receptor γ agonists).

Drugs with actions dependent on the gastrointestinal tract

Drugs that mediate their effect through the gastrointestinal tract include α-glucosidase inhibitors that slow glucose absorption by delaying degradation of complex carbohydrates in the gastrointestinal tract,99 pramlintide, which slows gastric emptying and thus delays glucose absorption;100 and the bile-acid-binding resin colesevelam, which lowers cholesterol and modifies release of other gastrointestinal peptides that can reduce plasma concentrations of glucose.89

Incretin-related products are designed to mimic or augment the action of GLP-1 and GIP, which are released by the intestine. GLP-1 receptor agonists are peptides with longer half-lives than GLP-1, whereas dipeptidyl peptidase 4 (DPP4) inhibitors block the action of DPP4, which is responsible for rapid degradation of GLP-1 and GIP.94 Improvement of the pharmacokinetics and pharmacodynamics of incretin-based drugs is under investigation to reduce dosing and to improve glucose control.95 Although not completely understood, infusion of large doses of GLP-1 intravenously can normalise glucose concentrations with less nausea or vomiting—adverse effects that can be dose limiting and prevent normalisation of glucose concentrations—than for subcutaneous administration.96,97 Whether new drugs can further improve glucose lowering and reduce nausea and vomiting remains unknown. In addition to the clear effect of these drugs on improvement of glycaemia, incretin-related products might also have beneficial effects on the cardiovascular system,98 although findings from the first two of a series of intervention studies showed a neutral effect.99,100Incretin-related medications have been purported to increase the risk of acute pancreatitis; this suggestion is based on findings from studies that used the inherently biased pharmacovigilance and administrative databases.101

More recently, GLP-1 receptor agonists and DPP4 inhibitors have been postulated to cause malignant transformations in the pancreas. However, this suggestion was based on histological assessments of a very small number of samples from brain-dead organ donors that were inadequately matched with controls for several crucial variables.102,103

Importantly, despite have been unsuccessful because of adverse effects or negligible therapeutic efficacy, several are very well accepted and are used worldwide. The mode of action for most of these drugs has been reported (figure 3). However, individual responses to these drugs can differ greatly, probably as a result of the heterogeneous nature of the pathophysiology of type 2 diabetes. The appendix provides further discussion on drugs that have been widely available for more than a decade (eg, sulfonylurea antidiabetics, biguanide antidiabetics, α-glucosidase inhibitors, and peroxisome proliferator-activated receptor γ agonists).

Treatment of type 2 diabetes

Oral and injectable drugs: present knowledge, lessons learned, and implications for the future

The increasing prevalence of type 2 diabetes has stimulated development of many new approaches to safely treat hyperglycaemia (figure 3). The aim of these therapies is to reduce and maintain glucose concentrations as close to normal for as long as possible after diagnosis (panels 1, 2), and thereby prevent development of complications. Although some therapies obtained through these assessments could provide the level of detail needed to establish the mediator (or mediators) of the feedback loop that interconnects β cells with insulin-sensitive tissues, and help to unravel the heterogeneity of the disease. Furthermore, these assessments should complement and advance present understanding of the best approaches to treat the dysregulated metabolic milieu in type 2 diabetes, which includes not only glucose but also fatty acids and aminoacids.

Figure 3: Drugs to treat type 2 diabetes

(A) The rate of introduction of new classes of drugs has accelerated during the past 20 years. Two classes (animal insulin and inhaled insulin; red) are essentially no longer available as therapeutics. (B) Different classes of drugs act on different organ systems. Insulin is a replacement for the natural product of islet β cells. Classic organ systems that have been targeted for decades comprise the pancreatic islet, liver, muscle, and adipose tissue. Non-classic targets have been focused on recently, and include the intestine, kidneys, and brain. DPP4 = dipeptidyl peptidase 4. SGLT2 = sodium–glucose co-transporter 2. GLP-1 = glucagon-like peptide 1.

See Online for appendix

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publicity received by this report, after a full assessment of the data the European Medicines Agency indicated that they were insufficient to support any causal association between these drugs and pancreatic cancer.104

**Inhibitors of sodium–glucose co-transporter 2**
The kidneys not only excrete and reabsorb glucose, but also produce glucose through gluconeogenesis.105 Generally, the quantity of glucose filtered does not exceed the kidneys’ threshold to reabsorb it, and thus little appears in urine. The finding that sodium–glucose co-transporter 2 (SGLT2) reabsorbed glucose from urine led to the development of inhibitors of this transporter to increase urinary glucose excretion.106,107 Two, dapagliflozin and canagliflozin, were recently introduced to market, and others are under clinical investigation. These drugs effectively reduce plasma glucose, bodyweight, and blood pressure. However, the increase in urinary glucose is associated with a five times higher rate of genital mycotic infections, and a 40% increase in infections of the lower urinary tract, compared with active comparators;108 additionally, these drugs cause unexplained, although slight, increases in LDL and HDL cholesterol.109 The increase in infections, and the potential effect on outcomes for cardiovascular disease (if unfavourable changes in LDL cholesterol outweigh favourable changes in HDL cholesterol), might reduce acceptance of these drugs by patients and health-care providers. Long-term studies that are in progress (eg, ClinicalTrials.gov identifiers NCT01032629, NCT01131676, and NCT01730534) will measure the cardiovascular safety of this class of glucose-lowering drugs.

**Drugs acting through the CNS**
Although the brain is crucial to the regulation of glucose metabolism, development of approaches that act centrally to reduce glucose concentrations has been difficult. The dopamine-receptor agonist bromocriptine is the only approved drug to regulate glucose metabolism that acts centrally, based on the notion that it restores circadian rhythm.110 Circadian rhythm is established partly by clock genes that are expressed centrally and in peripheral tissues, and affects several organ systems associated with metabolism.61 Other drugs that reduce glucose concentrations through

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**Panel 1: Oral drugs approved for treatment of hyperglycaemia in type 2 diabetes**

- **Second-generation sulfonylurea antidiabetics**
  - Glibenclamide (also known as glyburide)
  - Gliclazide
  - Glimepiride
  - Glipizide

- **Biguanide antidiabetics**
  - Metformin

- **Peroxisome proliferator-activated receptor γ agonists (thiazolidinedione antidiabetics)**
  - Pioglitazone
  - Rosiglitazone

- **α-glucosidase inhibitors**
  - Acarbose
  - Miglitol
  - Voglibose

- **DPP4 inhibitors**
  - Alogliptin
  - Linagliptin
  - Saxagliptin
  - Sitagliptin
  - Vildagliptin

- **SGLT2 inhibitors**
  - Canagliflozin
  - Dapagliflozin

- **Glinides**
  - Nateglinide
  - Repaglinide

- **Bile-acid-binding resins**
  - Colesevelam

- **Dopamine-receptor agonists**
  - Bromocriptine

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**Panel 2: Injectable drugs approved for treatment of hyperglycaemia in type 2 diabetes**

- **Islet amyloid polypeptide (amylin) analogues**
  - Pramlintide

- **GLP-1 receptor agonists**
  - Exenatide
  - Liraglutide
  - Lixisenatide

- **Rapid-acting and short-acting insulin**
  - Soluble insulin (also known as regular insulin)
  - Insulin aspart
  - Insulin glulisine
  - Insulin lispro
  - Insulin zinc-amorphous (also known as insulin semilente)

- **Intermediate-acting insulin**
  - Isophane insulin (also known as NPH insulin)
  - Insulin zinc (also known as insulin lente)

- **Long-acting insulin**
  - Insulin zinc-crystalline (also known as insulin ultralente)
  - Insulin detemir
  - Insulin glargine

GLP-1=glucagon-like peptide 1. NPH=neutral protamine Hagedorn. *Not all drugs available in all countries.
central actions often do so by reducing food intake and bodyweight—eg, GLP-1 receptor agonists, which effectively reduce bodyweight if they cross the blood–brain barrier.19

**Modified insulins**

Insulin therapies have advanced substantially in recent years, including discontinuation of animal forms and introduction of human forms. Modification of insulin has focused on changes to its pharmacokinetics, to make its action either more rapid (to better simulate the effect of insulin postprandially) or more prolonged, so as to reduce the need for twice-daily administration and create more flexibility with dosing.19 Whether these goals are always beneficial is debated.120 Insulin degludec (an insulin that forms soluble multihexamers on subcutaneous injection) has a longer duration of action than does insulin glargine, provides similar glucose control with less nocturnal hypoglycaemia,121 and has been approved in Europe and several other countries. However, the US Food and Drug Administration raised questions about the cardiovascular safety of insulin degludec and requested a cardiac safety study before reconsidering this insulin formulation for approval.122

Another long-duration insulin in development is insulin coupled with polyethylene glycol to delay absorption and clearance.124 Concentrated formulations of insulin (500 units per mL) are effective in a small number of very insulin-resistant patients;125 the effectiveness of this insulin when dosed two or three times a day is under investigation in a large trial (NCT01774968). Other areas of research interest include formulation of insulin for delivery by other routes and to reduce the risk of hypoglycaemia. Although inhaled insulin was expected to be revolutionary, difficulties in the development of practical delivery devices and a possible increased risk of lung carcinoma mostly ended the pursuit of such an approach.126 Oral formulations are also challenging, because of the need to avoid destruction of insulin by intestinal secretions and simultaneously deliver a predictable amount of insulin to plasma from the intestinal tract.127 With the emergence of treatment approaches that aggressively reduce glucose concentrations, so-called smart insulins are being developed that are dependent on ambient glucose concentration. These insulin formulations become active when glucose concentrations are raised; increased glucose competes with glycosylated insulin for binding to a lectin, thereby freeing insulin—an effect that would not occur if glucose concentrations were below normal.128 This technology is underdeveloped, but could provide an interesting alternative if successful in clinical development. Insulin molecules that are modified for liver selectivity are also under investigation; in human beings, they provided improved glycaemic control with fewer adverse effects, particularly hypoglycaemia.129

**Future developments in mostly untested areas**

Because available treatments at present do not easily achieve and maintain normal concentrations of glucose as β-cell function progressively decreases, new approaches are being developed (table 1), which represent mostly untested mechanisms.

**Treatment and prevention: goals and outcomes of clinical trials**

**The present situation**

In 1998, investigators of the landmark UKPDS trial143 reported that improved glucose control (mainly with sulfonylurea antidiabetics and insulin) reduced microvascular complications in recently diagnosed patients with type 2 diabetes. The primary analysis did not show a clear benefit for macrovascular disease, and thus four large intervention studies were designed to examine the effect of more intensive lowering of glucose for cardiovascular outcomes.

Insulin was a major component of the glucose-lowering interventions used in the ACCORD,144 VADT,145 and ORIGIN trials, whereas the ADVANCE study146 used a regimen based on the sulfonylurea antidiabetic gliclazide. Intensive glucose lowering did not reduce cardiovascular events in any of these studies, and indeed in susceptible patients might have been harmful. Analyses from ACCORD suggested that the patients who were at greatest risk of an adverse outcome from aggressive glucose lowering had a long duration of diabetes, poor glucose control at time of commencement of intensive insulin therapy, and did not have an immediate glucose-lowering response.148 Similar to findings from UKPDS, findings from ACCORD showed that improved glucose control reduced microvascular complications;149 however, these positive findings need to be balanced against the potential harmful effects of intensified therapy on cardiovascular outcomes. A similar microvascular benefit was shown by findings from ADVANCE, with the magnitude of effect related to the degree of glucose control, and affecting mostly renal outcomes (essentially as a result of reductions in microalbuminuria).150 Findings from ORIGIN showed no evidence of an increased risk of cancer for insulin glargine,146 despite suggestions from findings of pharmacovigilance studies that insulin could promote cancer.150 These findings of no effect of insulin therapy on cancer is consistent with a report that serum samples from patients with type 2 diabetes, treated with insulin glargine, activated insulin receptors A and B similarly to isophane insulin (also known as neutral protamine Hagedorn insulin), and did not increase signalling through the IGF-1 receptor.151 Thus, on the basis of five separate studies, present approaches to intensify glucose control are valuable to reduce microvascular complications but are not effective to reduce cardiovascular events, and are possibly even harmful in patients with advanced type 2 diabetes. Similar conclusions were reached by investigators of two meta-analyses that included these and other
These differences in cardiovascular outcomes emphasise the need for individualised targets for glucose control, as recommended in a position statement by the American Diabetes Association and the European Association for the Study of Diabetes on treatment of type 2 diabetes. Addressing of concomitant cardiovascular risk factors (eg, LDL cholesterol and blood pressure) could be more effective, and is consistent with vascular risk factors (eg, LDL cholesterol and blood type 2 diabetes). Addressing of concomitant cardiovascular risk factors (eg, LDL cholesterol and blood type 2 diabetes) is recommended in a position statement by the American Diabetes Association and the European Association for the Study of Diabetes on treatment of type 2 diabetes.

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<td>GPR119</td>
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<td>Liver-derived proteins, including betatrophin</td>
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<td>FOXO1</td>
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Table 1: Selected therapeutic targets of largely untested mechanisms for type 2 diabetes

Because lifestyle changes to reduce bodyweight have always been an important therapy for type 2 diabetes, investigators of Look AHEAD trial examined the effect of weight reduction (achieved by an intensive lifestyle intervention) on cardiovascular events. Despite differential weight loss for more than 10 years and improvements in many cardiovascular risk factors (including blood pressure and lipids), lifestyle change did not reduce cardiovascular events compared with diabetes support and education (control group). This finding might have been because large proportions of participants in both groups received medical treatment for these risk factors. However, participants in the group receiving lifestyle treatment showed a greater improvement in weight, blood pressure, and lipids.
intensive lifestyle intervention who had a history of a cardiovascular event at baseline had a tendency for an increased risk of a subsequent cardiovascular event;[26] a similar finding was reported in ACCORD.[30] Several other findings from Look AHEAD are worthy of comment. First, participants in the weight-loss group were more likely to achieve either partial or complete remission of diabetes,[37] had better glucose control needing fewer glucose-lowering drugs (including insulin), and were more likely to achieve a glycated haemoglobin \(A_g\) measurement of less than 7% (53 mmol/mol) than were those in the control group.[38] However, despite weight loss and addition of drugs, patients in the treatment group had similar progression of diabetes to that of the control group—ie, with continuous increases in glycated haemoglobin \(A_g\).[35] Second, lifestyle change slowed progression of nephropathy. Third, other health outcomes associated with better quality of life—eg, sleep apnoea[39] and mobility[40]—improved. Thus, intensive lifestyle change in patients with type 2 diabetes has benefits, but unfortunately not for cardiovascular outcomes, which remain the major cause of premature mortality in type 2 diabetes.

In view of the fact that type 2 diabetes is a progressive disease due to advancing \(\beta\)-cell dysfunction, can new drugs slow loss of \(\beta\)-cell function to provide durable glucose control? In the ADOPT study, recently diagnosed and previously untreated patients were given 4 years of monotherapy with glibenclamide, metformin, or rosiglitazone. Glibenclamide produced the largest initial reduction in glycaemia, but provided poorest maintenance of overall glucose control. Whereas the onset of glucose lowering with the other two drugs was slower than for glibenclamide, it was most sustained with rosiglitazone, with intermediate maintenance of glucose control with metformin, which was mostly related to effect on \(\beta\)-cell function.[161] Whether recently introduced drugs will maintain glucose control over the long term remains to be established. Limited data from a few patients suggest that incretin-based therapies, which are purported to improve \(\beta\)-cell health, could have such a benefit.[42]

Strategies to slow disease progression have also focused on people with impaired glucose tolerance or impaired fasting glucose because of their high risk of development of type 2 diabetes. Several studies have examined the ability of lifestyle modification and drugs to slow progression to diabetes (table 2). Findings from these trials have nearly all shown a benefit, with lifestyle modifications being more efficacious than any drug, with the exception of the thiazolidinedione antidiabetics.[160-171] Findings from prolonged follow-up showed that in some instances the benefit of treatment was retained for 10 years or more,[176-179] and could reduce risk of development of severe retinopathy.[79] In the DPP study,[180] restoration of individuals to normal fasting and 2 h glucose concentrations only once during the intervention phase was associated with a reduced rate of subsequent diabetes, mostly as a result of improved \(\beta\)-cell function. A question that has largely gone unanswered is whether the interventions actually alter the natural history of the disease, or simply mask the development of diabetes as a result of earlier commencement of treatment.[31] Only reports of the effects of troglitazone in DPP[172] and insulin glargine in ORIGIN[184] suggest a residual benefit after prolonged withdrawal of the intervention. However, despite good rationale for approval of interventions to delay the onset of diabetes,[32] no drug has yet received official sanction as a preventive treatment.

Finally, whereas type 2 diabetes mostly affects adults, sadly it is now emerging in youth. The pathogenesis of the syndrome in children is also crucially established by loss of \(\beta\)-cell function, with the degree of residual \(\beta\)-cell function determining glucose control in recently diagnosed patients.[33] The TODAY study[185] examined the effect of lifestyle and drugs in a young cohort with diabetes duration of less than a year, and found glycaemia to be best managed by the combination of rosiglitazone and metformin, with the addition of lifestyle to metformin being no better than metformin alone. The disease’s course in young people seems to be more aggressive than in adults, with the differential effect of interventions being the result of a greater improvement in \(\beta\)-cell function.[34] Further analyses from TODAY showed that in young people with type 2 diabetes, dyslipidaemia[186] and hypertension[187] are common and worsen over time. Both microalbuminuria and retinopathy increase with diabetes duration, and severity is related to glycaemic control.[188,189] These findings provide much-needed insights, and will certainly give rise to additional investigations into better treatments for type 2 diabetes in youth. Hopefully, good alternatives will be found, because the very high morbidity in young people has major implications for their quality of life as the duration of disease lengthens and complications develop.

What does the future hold?

Several of these studies are following up participants for outcomes relevant to type 2 diabetes. In DPP, conversion from impaired glucose tolerance to diabetes has been diagnosed within 6 months; findings from this study will provide a better understanding of the natural history of microvascular and macrovascular complications, and help to establish whether some of these complications (eg, retinopathy) develop before the onset of diagnostic hyperglycaemia. In both DPP and Look AHEAD, assessment of the decrease in longitudinal cognitive function will provide insight into this underappreciated adverse outcome of hyperglycaemia. Passive follow-up of participants from ORIGIN, ADVANCE, and TODAY will inform as to whether improved glucose control provides any beneficial legacy (so-called metabolic memory) on vascular disease, as was suggested initially by findings from the follow-up of patients with type 1 diabetes in the DCCT study,[188] and subsequently from the follow-up of...
UKPDS. Because improved glucose control reduces microvascular complications, and greater progression of retinopathy is associated with increased cardiovascular disease, a beneficial effect on cardiovascular outcomes might also be observed in these studies.

Cardiovascular safety of glucose-lowering drugs has become an essential requirement for their registration, and large studies of incretin-based therapies (NCT00790205, NCT00968708, NCT01107886, NCT01144338, NCT01147250, NCT01179048, NCT01243424, and NCT01394952) and SGLT2 inhibitors (NCT01032629, NCT01131676, and NCT01730534) are underway. The results of the SAVOR-TIMI 53 (NCT01107886) and EXAMINE (NCT00968708) studies were recently reported, and showed no increased risk of cardiovascular events with the DPP4 inhibitors saxagliptin and alogliptin. Collectively, the studies examining GLP-1 receptor agonists and DPP4 inhibitors will also provide an unbiased assessment of the possible increased risk of acute pancreatitis and malignant transformation in the pancreas with these drugs. Although the number of pancreas-related events in SAVOR-TIMI 53 and EXAMINE were too small to be definitive, there was no evidence for a marked excess of such events with either drug. One of these long-term studies (NCT01243424) directly compares a DPP4 inhibitor to glimepiride, and will provide insight into whether sulfonylurea antidiabetics...

<table>
<thead>
<tr>
<th>Study groups and number of participants</th>
<th>Average duration of follow-up (years)</th>
<th>Incidence of diabetes in control or placebo group (per 100 person-years)</th>
<th>Relative risk reduction (%)</th>
<th>p value</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lifestyle</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Da Qing163 Control (133), diet (130), exercise (141), diet and exercise (126)</td>
<td>6</td>
<td>15</td>
<td>7</td>
<td>31% (control vs diet); 46% (control vs exercise); 42% (control vs diet and exercise)</td>
<td>all &lt;0.05</td>
</tr>
<tr>
<td>Finnish Diabetes Prevention Study164 Control (257), lifestyle (265)</td>
<td>3</td>
<td>2</td>
<td></td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>US Diabetes Prevention Programme165 Placebo (1082), lifestyle (1079)</td>
<td>2</td>
<td>8</td>
<td></td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Indian Diabetes Prevention Programme166 Control (136), lifestyle (133)</td>
<td>2</td>
<td>5</td>
<td></td>
<td>18</td>
<td>3</td>
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<td><strong>Medication</strong></td>
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<tr>
<td>US Diabetes Prevention Programme165 Placebo (1082), metformin (1073)</td>
<td>2</td>
<td>8</td>
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<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Indian Diabetes Prevention Programme166 Control (136), metformin (133)</td>
<td>2</td>
<td>5</td>
<td></td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>Nepi Antidiabetes Study182 Placebo (138), glimepiride (136)</td>
<td>3</td>
<td>7</td>
<td></td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>STOP-NIDDM184 Placebo (215), acarbose (714)</td>
<td>3</td>
<td>3</td>
<td></td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>XENDOS185 Placebo (344), orlistat (350)</td>
<td>4</td>
<td>0</td>
<td></td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>NAVIGATOR181 Placebo (4661), nateglinide (4645)</td>
<td>5</td>
<td>0</td>
<td></td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>ORIGIN186 Placebo (719), insulin glargine (737)</td>
<td>6</td>
<td>2</td>
<td></td>
<td>5</td>
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<td><strong>Combination therapy</strong></td>
<td></td>
<td></td>
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<tr>
<td>Indian Diabetes Prevention Programme166 Control (136), lifestyle plus metformin (129)</td>
<td>2</td>
<td>5</td>
<td></td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>CANOE187 Placebo (104), lifestyle plus rosiglitazone (103)</td>
<td>3</td>
<td>9</td>
<td></td>
<td>10</td>
<td>1</td>
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When not available, incidence rates were calculated from the proportion of individuals who had reached the primary outcome divided by the average duration of follow-up. NS=not significant.

Table 2: Results of intervention studies to prevent development of type 2 diabetes in people with impaired glucose tolerance
confer an increased risk of cardiac events, a question raised by findings from the University Group Diabetes Program more than 40 years ago.\textsuperscript{192,193} Furthermore, these studies should provide information about whether incretin-based drugs actually protect against cardiovascular disease, as suggested by findings from meta-analyses of phase 2 and 3 studies.\textsuperscript{79,155} Finally, although not designed specifically to do so, these studies will provide clues as to whether incretin-based therapies and SGLT2 inhibitors provide more durable glucose control.

What else is needed? Although present treatment algorithms are less prescriptive than were earlier algorithms, and advocate a more personalised approach to the choice of drugs and treatment targets for type 2 diabetes,\textsuperscript{154} an important question that still remains is what drug to add after metformin. Present treatment algorithms are based mostly on studies done by pharmaceutical companies, which typically do not compare more than two drugs and are short term. The GRADE trial\textsuperscript{196} will compare head-to-head the effect on glycemic control, and include reduced weight and glucose control, and include reduced cardiovascular events and mortality.\textsuperscript{198–201} However, these hypotheses are based on results from the SOS study,\textsuperscript{198–201} in which participants were not randomised and the control group was contemporaneously matched, only received conventional treatment, and differed by several characteristics at baseline. Thus, appropriately controlled studies comparing surgical and non-surgical interventions to produce weight loss are needed. Furthermore, long-term studies of the effect of so-called metabolic surgery, which focuses mainly on correction of metabolic abnormalities rather than weight loss (as does bariatric surgery),\textsuperscript{201} are needed to establish whether the progression of diabetes can be slowed or halted and whether adverse events as a result of the surgery reduce its usefulness. Clarification of the differential long-term positive and negative effects of simple restriction with banding versus the more complex bypass procedures would also be helpful.\textsuperscript{201}

**Conclusions**

In 1984, Asmal and Marble\textsuperscript{202} wrote that “despite the availability of oral hypoglycaemic drugs for nearly 30 years, their precise mode of action and role in the management of diabetes mellitus remains poorly defined and controversial”. Nearly 30 years after that statement, doctors and researchers still have a great deal to learn about the pathogenesis of type 2 diabetes and how best to use the therapies available, although great progress has been made in clarification of their modes of action. The next 30 years will hopefully provide the knowledge and approaches needed to reduce the global harm of type 2 diabetes, not only through management of the disorder more effectively with a combination of non-pharmacological and pharmacological approaches, but also through prevention of the disease and identification of new strategies to directly target its complications.

**Contributors**

SEK did the initial literature review and wrote first draft of this Review. MEC and SDP provided critical review and redrafting of the text and figures, and assisted with additional literature review.

**Conflicts of interest**

SEK has received honoraria for advisory work and lectures from Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Genentech (Roche), GlaxoSmithKline, Intarcia, Janssen, Merck, Novo Nordisk, Receptos, and Takeda. MEC has received honoraria for advisory work and lectures from AbbVie, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Merck, Novo Nordisk, and Takeda. SDP has received honoraria for advisory work and lectures from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Intarcia, Janssen, Merck Sharpe and Dohme, Novartis, Novo Nordisk, Roche Diagnostics, Sanofi-Aventis, and Takeda; and research support from Bristol-Myers Squibb, Merck Sharpe and Dohme, Novartis, and Novo Nordisk.

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