PATHOPHYSIOLOGY AND TREATMENT OF TYPE 2 DIABETES: PERSPECTIVES ON THE PAST, PRESENT AND FUTURE

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Abstract

Normal regulation of glucose metabolism is determined by a feedback loop involving the islet β-cell and insulin-sensitive tissues in which tissue sensitivity to insulin determines the magnitude of the β-cell response. When insulin resistance is present, the β-cell maintains normal glucose tolerance by increasing insulin output. It is only when the β-cell is incapable of releasing sufficient insulin in the presence of insulin resistance that glucose levels rise. While β-cell dysfunction has a clear genetic component, environmental changes play a vital role. Modern approaches have also informed regarding the importance of hexoses, amino acids and fatty acids in determining insulin resistance and β-cell dysfunction as well as the potential role of alterations in the microbiome. A number of new treatment approaches have been developed, but more effective therapies that slow the progressive loss of β-cell function are needed. Recent clinical trials have provided important information regarding approaches to prevent and treat type 2 diabetes as well as some of the adverse effects of these interventions. However, additional long-term studies of medications and bariatric surgery are required in order to identify novel approaches to prevention and treatment, thereby reducing the deleterious impact of type 2 diabetes.

Keywords

type 2 diabetes; impaired glucose tolerance; impaired fasting glucose; pathophysiology; β cell; insulin secretion; insulin resistance; α-cell; glucagon secretion; genetics; environment; inflammation; microbiome; treatment; medications; prevention; clinical trials; bariatric surgery

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Type 2 Diabetes: The Epidemic of Our Time

The worldwide explosion of obesity has resulted in an ever-increasing prevalence of type 2 diabetes, a non-communicable disease that has become a scourge of our time, knows no boundaries and currently affects over 370 million people \(^1\). Without more concerted efforts addressing the pathogenesis and treatment of this syndrome, the deleterious macrovascular and microvascular outcomes will remain a major burden for decades to come. This perspective examines aspects of the pathogenesis of type 2 diabetes and its treatment, considering also future needs if we are going to reverse what is clearly the most damaging consequence of obesity.

Pathogenesis of Type 2 Diabetes: From Past to Present Day and the Future

The Past: Identification of \(\beta\)-cell Dysfunction and Insulin Resistance

Development of the insulin radioimmunoassay led to the identification that individuals with “early maturity onset diabetes” produced insulin and secreted this hormone in response to nutrient ingestion \(^2\). Subsequently, it was shown that these individuals manifest a defect in the ability of the islet \(\beta\)-cell to respond to intravenous secretagogues including glucose \(^3\).

In these earlier days it was demonstrated that these individuals also did not respond well to insulin \(^4\) and were thus deemed to be “insulin-insensitive”. It was subsequently shown that this contributed to increased glucose production by the liver and decreased glucose uptake in muscle and adipose tissue \(^5\). Today we recognize that a proportion of these abnormalities are explained by adiposity, especially that located within the intra-abdominal cavity \(^6\).

The Present: Feedback Regulation Identifies the Critical Role of the \(\beta\)-cell in Glucose Homeostasis

The relative importance of insulin resistance and \(\beta\)-cell dysfunction in the pathogenesis of type 2 diabetes was debated for a long time, with many considering that insulin resistance was the primary abnormality with the inability to secrete insulin a late phenomenon \(^5\). This notion changed with the demonstration in humans that, as with most endocrine systems, a feedback loop operates to ensure integration of glucose homeostasis and maintenance of glucose in a tight range \(^7\).

This feedback loop relies on crosstalk between the \(\beta\)-cell and the insulin sensitive tissues (Figure 1A). Insulin released in response to \(\beta\)-cell stimulation mediates the uptake of glucose, amino acids and fatty acids by insulin-sensitive tissues. In turn, these tissues feedback information to the islet regarding their need for insulin, the mediator of which has not yet been identified but is likely to involve integration between the brain and humoral systems. When insulin resistance is present, as seen most commonly with obesity, the \(\beta\)-cell increases its insulin output to maintain normal glucose tolerance (Figure 1B). However, when the \(\beta\)-cell is incapable of this task, the result is an elevation in plasma glucose (Figure 1C).

While the distinction between impaired fasting glucose and/or impaired glucose tolerance, at times together referred to as prediabetes, and diabetes is determined by fasting and 2-hour
glucose levels following a standardized oral glucose load, the reality is that these disturbances are a continuum in which the magnitude of the reduction in β-cell function determines the degree of elevation in plasma glucose. Insulin resistance is already well established when impaired glucose tolerance is present and the increase in glucose, even across the normal range, is due to a continuous decline in β-cell function. Further progressive deterioration of β-cell function accounts for the evolving natural history of the disease from impaired glucose tolerance to type 2 diabetes.

Diminished β-cell function is already present in groups known to be at increased risk of diabetes including first-degree relatives of individuals with diabetes, women with gestational diabetes or polycystic ovary syndrome and older individuals and underlies the progression to diabetes. Further, it has been shown that β-cell function is heritable and critically determines glucose intolerance and type 2 diabetes in different racial and ethnic groups.

Despite the advances in our understanding of the relative importance of insulin resistance and β-cell dysfunction in the pathogenesis of type 2 diabetes and high-risk states, it is clear that the disease process is heterogeneous, including other pathogenic factors discussed subsequently.

The Present: Genes, Environment and the Development of Type 2 Diabetes

Genes and the environment together are important determinants of insulin resistance and β-cell dysfunction (Figure 2). As our gene pool has not changed in recent times, environmental changes have been critical in determining the type 2 diabetes epidemic.

Advances in technology and analytical approaches have led to the discovery of genes linked to type 2 diabetes. Using the candidate gene approach, PPARγ was the first gene identified. Since then, using largely genome-wide association studies (GWAS), over 50 gene loci have been linked to type 2 diabetes. Further, 53 loci have been linked to glucose and insulin concentrations, of which 33 also link to type 2 diabetes, but do not always associate with both fasting and 2-hour glucose. While a few loci are associated with obesity and insulin resistance, the vast majority are linked to the β-cell. Some are related to known gene products, but for most of these genes the products have not yet been definitively identified. Together these genes do not appear to explain much of the genetic basis of the disease with the use of genotype risk scores only slightly improving prediction of subsequent diabetes compared to common clinical risk factors.

Aside from the obvious increases in caloric intake and decreased energy expenditure, other environmental factors appear important. Nutrient composition, specifically increased amounts of dietary fat and saturated fat are important in determining the development of obesity, insulin resistance, β-cell dysfunction and glucose intolerance. Further, an aging associated reduction in the β-cell’s responsiveness to carbohydrate in part underlies the decline in glucose tolerance with aging. The in utero environment, determined in part by the mother’s body habitus, may well produce epigenetic and gene expression changes that determine the risk of the offspring to development of obesity and type 2 diabetes. Recent
discussion has also focused on the role of environmental chemicals in the obesity and diabetes epidemics\textsuperscript{27}.

**The Present: Further Delineation of the Roles of Reduced β-cell Number and α-cell Dysfunction**

A reduced number of β-cells is a longstanding observation in type 2 diabetes\textsuperscript{28}, and this has recently again become of interest\textsuperscript{29–31}. The basis for this loss is multifactorial, and includes glucolipotoxicity\textsuperscript{32} and amyloid deposition that result in β-cell apoptosis through oxidative as well as endoplasmic reticulum stress\textsuperscript{31}. This loss is not counterbalanced by the development of new β-cells as the human pancreas appears incapable of renewing these cells beyond the age of 30\textsuperscript{33}. While a reduction in β-cell mass exists in type 2 diabetes, it is clear that the magnitude of this abnormality is insufficient to explain the degree of impairment in insulin release. Whether the underlying defect in β-cell function is important as an initiator of the process of β-cell loss and/or whether the increasing secretory demand on each individual β-cell as cell number diminishes determines ongoing β-loss remains to be defined. Elucidating the relative importance of β-cell function versus mass could have important implications for the development of approaches to preserve β-cells and help maintain or improve glucose tolerance.

While less well studied, dysregulated α-cell release of glucagon, manifest as increased fasting glucagon concentrations and a failure to adequately suppress glucagon release following meal ingestion, contributes to the development of hyperglycaemia\textsuperscript{34}. Whether this represents a primary change in the α-cell or is secondary to an abnormality in β-cell function is not yet resolved. It is known that islet blood flows from the β- to the α-cell and then to the somatostatin producing δ-cell\textsuperscript{35}, and that the high concentrations of insulin bathing the α-cell are capable of suppressing glucagon release\textsuperscript{36}. Other β-cell products such as zinc, γ-amino-butyric acid (GABA) or glutamate may also regulate glucagon release\textsuperscript{36}. Approaches that diminish glucagon release or impair its action to raise glucose levels may well represent additional therapeutic alternatives for type 2 diabetes\textsuperscript{34}.

**The Present: Important Roles of the Intestine and Brain**

The gastrointestinal tract produces a variety of peptides, not all of which directly modulate nutrient absorption. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), collectively known as the “incretins”, act on the pancreatic islet. GLP-1 is the more important of these hormones acting on both β- and α-cells to enhance insulin and suppress glucagon secretion, respectively\textsuperscript{37}. Plasma GLP-1 levels are not in general different in individuals with normal glucose tolerance, impaired glucose tolerance or type 2 diabetes\textsuperscript{38}. Therefore, the problem has to be that the β-cell response to GLP-1 following meal ingestion is deficient, as shown following intravenous administration of GLP-1 under controlled conditions\textsuperscript{39}. This deficient response is in keeping with a more global deficiency in β-cell responsiveness to numerous secretagogues including sulphonylureas, amino acids, and β-adrenoreceptor agonists\textsuperscript{40}. While GLP-1 acts directly on the α-cell to suppress glucagon release, the relative impact of this mechanism versus modulation by β-cell products remains uncertain both in healthy individuals and in the setting when glucagon is inadequately suppressed during a meal in type 2 diabetes. It is also interesting to note that
increased levels of GLP-1 have been observed following bariatric surgery and thought to explain many of the beneficial effects of the intervention, particularly in individuals with type 2 diabetes\textsuperscript{41}. However, this is not the sole mechanism by which glucose lowering may occur following this surgical procedure\textsuperscript{41,42}.

Bile acids are also important in regulating glucose metabolism. They are endogenous ligands of the farnesoid X receptor (FXR), their activation of FXR resulting in the release of fibroblast growth factor (FGF) \textsuperscript{19,43}. Bile acids also activate the G-protein-coupled receptor TGR5 (also known as GPR131) located on intestinal L-cells, leading to GLP-1 secretion\textsuperscript{44}. In humans, infusion of bile acids intraduodenally dose-dependently increases plasma levels of FGF19, with smaller effects on GLP-1 and CCK\textsuperscript{45}. As FGF19 has insulin-like effects inducing glycogen and protein synthesis while inhibiting glucose production\textsuperscript{43}, the biliary system may have as yet underappreciated effects to modulate glucose homeostasis.

The intestinal microbiome also appears to be important in the pathophysiology of type 2 diabetes\textsuperscript{46}. The microbiome contains about 100 times the genetic information found in the human genome and together these comprise 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 role in a number of conditions including obesity and type 2 diabetes, although which bacterial species may be involved in altering human metabolism remains to be determined\textsuperscript{47}. Two recent studies have used faecal samples to suggest that functional changes in the gut microbiome might be directly linked to the development of type 2 diabetes\textsuperscript{48,49}; however, the metagenomic markers differ between populations suggesting that their ability to predict the development of diabetes will likely vary\textsuperscript{49}. A recent proof-of-concept study demonstrated an improvement in insulin sensitivity in individuals with the metabolic syndrome six weeks after the infusion of intestinal microbiota from lean individuals\textsuperscript{50}. Lastly, there is also the possibility for different gut flora to impact nutrient absorption since in humans the load of nutrients can in a short time alter the faecal bacterial community\textsuperscript{51}.

The nervous system is another key regulator of metabolic processes. Both sympathetic and parasympathetic nervous systems control glucose metabolism directly through neuronal input and indirectly via the circulation to influence insulin and glucagon release\textsuperscript{52} and hepatic glucose production\textsuperscript{53}. In humans, the vagus is important in regulating the islet as severing this nerve results in impaired insulin secretion\textsuperscript{54}. The hypothalamus has been identified as an important integrator since ablation of the hypothalamus in rats results in dysregulation of the β-cell and the development of hyperinsulinaemia\textsuperscript{55}. This brain region also regulates hepatic glucose production via the action of insulin, glucose and fatty acids\textsuperscript{56–58}. Insulin action at this site is also vital in regulating body weight, with a diminished effect leading to obesity\textsuperscript{59}. More recently it has been demonstrated that inflammation-induced neuronal injury occurs rapidly in rodents on a high fat diet and imaging in humans suggests structural changes in the hypothalamus in keeping with gliosis in obese compared to lean individuals\textsuperscript{60}. Finally, clock genes located in the brain are important in determining circadian rhythmicity and, together with sleep, have become a focus of investigation as it is clear that alterations in diurnal patterns and quality of sleep can have important effects on metabolic processes\textsuperscript{61,62}.
The Present: Systemic and Islet Inflammation

Obesity is frequently characterized by systemic inflammation and preclinical evidence links systemic inflammation to β-cell dysfunction. Markers of systemic inflammation, including C-reactive protein (CRP) and its upstream regulator interleukin-6 (IL-6), exhibit cross-sectional relationships with insulin sensitivity and β-cell function. Lifestyle change and pharmacological agents 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 intra-islet immune response, the strongest support being for a role for interleukin-1β (IL-1β). Glucose and fatty acids increase IL-1β production in islets, and naturally occurring antagonists, particularly IL-1 receptor antagonist (IL-1Ra), balance and regulate the action of IL-1β in islets and other tissues. Circulating levels of IL-1β and IL-1Ra are elevated in type 2 diabetes and lower levels of IL-1Ra may predict who maintains better β-cell function after an intervention to decrease islet inflammation.

Expansion of adipose tissue is associated with the accumulation of activated macrophages that express a number of proinflammatory genes, including cytokines such as TNF-α that are released and have their major effect locally to impair insulin signalling. A feed forward process also comes into play in which activation of transcription factors begets further proinflammatory cytokine production. When the production of these cytokines is sufficient, they are released into the circulation where they can act at distant sites such as liver and skeletal muscle to worsen insulin resistance. A similar process can occur in the liver involving Kupffer cells, which are resident macrophages, and recruited macrophages. Hypothalamic inflammation is also felt to contribute to central leptin resistance and body weight gain.

The Future: Genetics, Epigenetics, and The Omics

While our understanding of the genetics of type 2 diabetes has advanced rapidly, much remains to be learned. How genes interact with the environment to determine the progressive loss of β-cell function remains unclear. It is possible that environmental factors and hyperglycaemia 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 the β-cell. Whether such changes contribute to the increased risk of developing type 2 diabetes and also to the progression of the disease will be of interest.

Finally, as we currently can only explain a small proportion of the risk of type 2 diabetes based on identified genetic loci, it is possible that the search for rarer variants by approaches such as exome sequencing may provide additional insights and possible therapies.

The “omics” include metabolomics, lipidomics, proteomics, genomics and transcriptomics. The findings made using these approaches are being integrated to better understand the pathophysiology of type 2 diabetes and the heterogeneity of responses to different glucose-lowering therapies. Using metabolomics and lipidomics, increases in branched-chain and aromatic amino acids have been shown to be associated with obesity and type 2 diabetes. A recent report also identified an increased risk of developing type 2 diabetes.
over a 7-year follow-up period with higher levels of certain 6-carbon sugars, amino acids and fatty acids as well as lower levels of other amino acids and fatty acids. Whether all or some of these substrate markers are associated with genetic determinants, dietary factors or the actions of gut microbes remains to be determined.

In the long run these new approaches should identify additional genes and metabolic markers, with the profiles obtained through these assessments perhaps providing the level of detail to solve the mystery of the mediator(s) of the feedback loop that interconnects the β-cell with insulin-sensitive tissues and help in unravelling the heterogeneity of the disease. Further, these assessments should complement and advance our current understanding of the best approaches to treat the dysregulated metabolic milieu of type 2 diabetes which, while primarily focused on glucose, clearly also involves fatty acids and amino acids.

**Therapeutic Options: From Then to Now and Beyond**

**Oral Agents and Injectables - Current Knowledge, Lessons Learned and Implications for the Future**

The increasing prevalence of type 2 diabetes has spurred the development of many new approaches to safely treat hyperglycaemia in order to lower and maintain glucose concentrations as close to normal for as long as possible after diagnosis and thereby prevent the development of complications (Figure 3A). While some have already fallen by the wayside because of unwanted adverse effects or minimal therapeutic efficacy, a number are very well accepted and utilized globally. For most of these medications, their mode of action has been elucidated. The organs on which many of them act primarily are depicted in Figure 3B. Individual responses to these medications may be quite different however, likely reflecting the heterogeneous nature of the pathophysiology of type 2 diabetes.

A list of the available agents within each class are provided in Table 1 with further discussion on medications that have been widely available for more than a decade such as sulphonylureas, biguanides, α-glucosidase inhibitors, and peroxisome proliferator-activated receptor (PPAR) γ agonists are addressed in the supplemental materials.

**Agents With Actions Dependent on the Gastrointestinal Tract**—Agents that mediate their effect through the gastrointestinal tract include the (i) α-glucosidase inhibitors that slow glucose absorption by delaying the degradation of complex carbohydrate in the gastrointestinal tract, (ii) pramlintide, which slows gastric emptying and thus delays glucose absorption, and (iii) bile acid binding resin colesevelam that lowers cholesterol and modifies the release of other gastrointestinal peptides that may act to lower plasma glucose.

In addition, incretin-related products are designed to mimic or augment the action of the peptides GLP-1 and GIP that are released by the intestine. The GLP-1 receptor agonists represent modifications aimed at prolonging their half lives, while dipeptidyl peptidase-4 (DPP-4) inhibitors block the action of this enzyme that is responsible for the rapid degradation of GLP-1 and GIP. Ongoing work is focused on trying to improve the pharmacokinetics and pharmacodynamics of incretin-based agents so that they can be dosed...
less frequently and provide superior glucose control\textsuperscript{91}. Interestingly, though not completely understood, infusion of large doses of GLP-1 intravenously can normalize glucose concentrations with relatively little nausea or vomiting\textsuperscript{92,93}, whereas subcutaneous administration is associated with these adverse effects that can be dose limiting and prevent normalization of glucose concentrations. Whether it will be possible to produce a more effective glucose-lowering agent with lesser degrees of nausea and vomiting remains unknown. In addition to their clear effect to improve glycemia, it has been suggested that incretin-related products may also have beneficial effects on the cardiovascular system\textsuperscript{94,95}, although a neutral effect has been reported by the first two of a series of intervention studies\textsuperscript{96,97}. Incretin-related medications have been purported to increase the risk of acute pancreatitis, which has been suggested by some but not all studies performed using largely the inherently biased pharmacovigilance and administrative databases\textsuperscript{98–101}. More recently it has been suggested that malignant transformation in the pancreas may also occur with GLP-1 receptor agonists and DPP-4 inhibitors. However, this suggestion was based on histological assessments of a very limited number of samples from brain dead, organ donors inadequately matched with controls for a number of critical variables\textsuperscript{102,103}. Importantly, despite the publicity this report has garnered, after a full assessment of these data, the European Medicines Agency recently indicated that they were insufficient to support any causal relationship between these agents and pancreatic cancer\textsuperscript{104}.

**Inhibitors of the Sodium-Glucose Transporter-2**—The kidney not only excretes and reabsorbs glucose, but also produces it via gluconeogenesis\textsuperscript{105}. Normally the quantity of glucose filtered does not exceed the kidney’s threshold to reabsorb it and thus little appears in the urine. The demonstration that an isoform of the sodium-glucose transporter, SGLT2, reabsorbs glucose from urine led to the development of inhibitors of this transporter to increase urinary glucose excretion\textsuperscript{106,107}. Two of them, dapagliflozin and canagliflozin, were recently introduced into the market and others are currently undergoing clinical testing. These agents effectively lower plasma glucose while simultaneously reducing body weight and blood pressure. However, the increase in urinary glucose is associated with a five-fold increase in genital mycotic infections and 40% increase in lower urinary tract infections compared to active comparators\textsuperscript{108} and these agents lead to unexplained increases in LDL- and HDL-cholesterol\textsuperscript{109}. Whether the increase in infections will limit acceptance of these agents by patients and healthcare providers alike remains to be seen, as does the potential impact on cardiovascular disease outcomes of the balance of potentially favourable HDL cholesterol changes versus the unfavourable LDL change. The cardiovascular outcomes from such medications will come from the current requirement for long-term studies demonstrating cardiovascular safety of glucose-lowering agents.

**Medications Acting Through the Central Nervous System**—While the brain is critical in regulating glucose metabolism, developing approaches that act centrally to lower glucose has proven difficult. The dopamine receptor agonist bromocriptine is the only approved medication that primarily acts centrally, based on the concept that it restores circadian rhythm\textsuperscript{110}. Circadian rhythm is determined in part by clock genes located centrally and in peripheral tissues, affecting a number of organ systems involved in metabolism\textsuperscript{61}. Whether new agents will be able to modify this system for greater benefit will be known in...
time. Other agents that lower glucose through central actions often do so by reducing food intake and body weight. The GLP-1 receptor agonists are an example, effectively reducing body weight if they cross the blood-brain barrier\textsuperscript{90}.

**Modified Insulins**—Recent times have seen an (r)evolution in the forms of insulin available for therapy, including discontinuation of animal forms and introduction of human forms. Modification of the molecule has focused on changing its pharmacokinetics to either make its action more rapid, in order to better simulate the effect of insulin post-prandially, or more prolonged, so as to reduce the need for twice daily administration and create more flexibility with dosing\textsuperscript{111}. Whether this is always beneficial is debated\textsuperscript{112}. Recently degludec, an insulin which forms soluble multihexamers on subcutaneous injection, has a duration of action longer than glargine, providing similar glucose control with less nocturnal hypoglycaemia\textsuperscript{113}, was approved in Europe and a number of other countries. However, the United States Food and Drug Administration (FDA) raised questions about its cardiovascular safety and requested a cardiac safety study before reconsidering this insulin formulation for approval. Another longer duration insulin in development will have insulin coupled to polyethylene glycol to delay its absorption and clearance\textsuperscript{114}. Recently, formulations of more concentrated (U500) insulin have proven effective in a limited number of very insulin resistant patients\textsuperscript{115}, and a large study is currently addressing the effectiveness of this insulin when dosed twice or three times a day (clinicaltrials.gov identifier NCT01774968). Work also continues on formulating insulin to deliver it by other routes and reduce the risk of hypoglycaemia. While inhaled insulin was expected to be revolutionary, difficulty in developing practical delivery devices and the unfavourable imbalance in the number of cases of lung carcinoma largely ended the pursuit of such an approach\textsuperscript{116}. An oral formulation is also a challenge given the need to avoid destruction of insulin by the intestinal secretions while simultaneously delivering a predictable amount from the intestinal tract to plasma\textsuperscript{117}. With the advent of more aggressive glucose lowering, “smart insulins” are being developed that are dependent on the ambient glucose concentration. These insulin formulations become active when glucose is elevated as the increased glucose competes with glycosylated insulin for binding to a lectin thereby freeing the insulin, an effect that would not occur when glucose levels are below normal\textsuperscript{118}. This technology is in its infancy, but could provide an interesting alternative should it make it through clinical development. Modified insulin molecules aimed at being more liver selective are also currently being developed and tested in humans in order to provide improved glycemic control with less adverse effects, particularly hypoglycaemia\textsuperscript{119}.

**Future Developments in Largely Untested Areas**—As the current treatment armamentarium does not readily attain and maintain normal glucose levels as \(\beta\)-cell function progressively declines, new and novel approaches are being developed. Table 2 lists selected therapeutic targets that represent largely untested mechanisms, some of which may turn out to be successful and others may prove less so.
Treatment and Prevention: Goals and Outcomes of Clinical Trials

Where Do We Stand Today?

In 1998, the landmark United Kingdom Prospective Diabetes Study (UKPDS) reported that improving glucose control primarily with sulphonylureas and insulin reduced microvascular complications in recently diagnosed patients with type 2 diabetes\textsuperscript{120}. The primary analysis did not show a clear benefit on macrovascular disease, and thus four large intervention studies were designed to examine the effect of more intensive glucose lowering on cardiovascular outcomes.

Insulin was a major component of the glucose-lowering interventions in the ACCORD (Action to Control Cardiovascular Risk in Diabetes)\textsuperscript{121}, VADT (VA Diabetes Trial)\textsuperscript{122} and ORIGIN (Outcome Reduction with an Initial Glargine Intervention)\textsuperscript{123} trials, while the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) study utilized a regimen based on the sulfonylurea gliclazide\textsuperscript{124}. In none of these studies did intensive glucose lowering reduce cardiovascular events, and indeed in the vulnerable patient may have been harmful. Analyses from ACCORD suggest that the individual likely to be at greatest risk of an adverse outcome to aggressive glucose lowering had a longer duration of diabetes, poor glucose control at the time of commencing intensive insulin therapy, and did not demonstrate an immediate glucose lowering response\textsuperscript{125}. ACCORD, like the UKPDS, demonstrated that improved glucose control reduced microvascular complications\textsuperscript{126}, but these positive findings must be balanced against the potential deleterious effect of intensified therapy on cardiovascular outcomes. Such a microvascular benefit was also shown in ADVANCE, the magnitude being related to the degree of glucose control and affecting largely renal outcomes (essentially a reduction in microalbuminuria)\textsuperscript{124}. Noteworthy from the ORIGIN study was the lack of evidence of an increased risk of cancer with glargine\textsuperscript{123}, despite suggestions from pharmacovigilance studies that insulin may promote cancer\textsuperscript{127}. This lack of an effect on cancer is in keeping with a recent report that serum from type 2 diabetic patients treated with glargine activates insulin receptors A and B similarly to NPH insulin and does not increase signalling through the IGF-1 receptor\textsuperscript{128}. Thus, based on five separate studies, it would seem that current approaches involving intensification of glucose control are valuable for reducing microvascular complications but are not effective in reducing cardiovascular events, possibly even being harmful in those with advanced type 2 diabetes. Similar conclusions were reached by two meta-analyses that included these and other studies\textsuperscript{129,130}. These differences in cardiovascular outcomes underscore the need for individualized glucose control targets as recently highlighted in the ADA/EASD position statement on the treatment of type 2 diabetes\textsuperscript{131}. It appears that addressing concomitant cardiovascular risk factors such as LDL-cholesterol and blood pressure may be more effective, and is consistent with the multifactorial approach in the Steno 2 Study that demonstrated a reduction in both cardiovascular and microvascular events which was sustained even after cessation of the initial glucose, blood pressure and lipid lowering regimens\textsuperscript{132}.

As lifestyle change to reduce body weight has always been a mainstay of type 2 diabetes therapy, the Look AHEAD (Action for Health in Diabetes) trial examined the effect on
cardiovascular events of weight reduction achieved by an intensive lifestyle intervention. Despite differential weight loss for over 10 years and improvements in many cardiovascular risk factors, including blood pressure and lipids, lifestyle change did not reduce cardiovascular events compared to diabetes support and education (control).\textsuperscript{133} This may have been because large proportions of subjects in both groups received medical treatment for these risk factors. Interestingly, those in the intensive lifestyle arm with a history of cardiovascular event at baseline demonstrated a tendency for an increased risk of a subsequent cardiovascular event\textsuperscript{133}, an observation similar to that in ACCORD\textsuperscript{121}. A number of other observations from Look AHEAD are worthy of comment. First, with weight loss a greater proportion of subjects achieved either partial or complete diabetes remission\textsuperscript{134}, improved glucose control required fewer glucose-lowering agents, including insulin, and a greater proportion of participants achieved a HbA1c <7\%\textsuperscript{135}. However, despite weight loss and addition of medications, the disease progressed based on a continuous increase in HbA1c\textsuperscript{133}. Second, lifestyle change did slow the progression of nephropathy. Third, other health outcomes associated with better quality of life improved, including sleep apnoea\textsuperscript{136} and mobility\textsuperscript{137}. Thus, intensive lifestyle change in patients with type 2 diabetes has benefits, but unfortunately not on cardiovascular outcomes which remain the major determinant of premature mortality in type 2 diabetes.

As type 2 diabetes is a progressive disease due to advancing β-cell dysfunction, the development of new medications raises the critical question as to whether the loss of β-cell function can be slowed to provide more durable glucose control. ADOPT (A Diabetes Outcome Progression Trial) compared four years of monotherapy with glibenclamide, metformin or rosiglitazone in recently diagnosed, drug-naïve individuals\textsuperscript{138}. Glibenclamide produced the greatest initial reduction in glycaemia, but was poorest in maintaining glucose control. Whereas the onset of glucose lowering with the other two medications was slower, it was most sustained with rosiglitazone, with metformin demonstrating an intermediate pattern. This differential effect was largely related to the impact on β-cell function\textsuperscript{11,138}. Whether the same holds true or not for more recently introduced agents over the long term remains to be fully answered. Limited data in a small number of subjects suggests that incretin-based therapies, which are purported to improve β-cell health, may have such a benefit\textsuperscript{139}.

Slowing disease progression has also focused on individuals with impaired glucose tolerance and/or impaired fasting glucose because of their high risk of developing type 2 diabetes. A number of studies have examined the ability of lifestyle and medications to slow progression to diabetes (Table 3). These trials have more or less uniformly demonstrated a benefit, with lifestyle more efficacious than all medications with the exception of the thiazolidinediones\textsuperscript{140–152}. Prolonged follow up showed that in some instances the benefit is retained for 10 years or more\textsuperscript{153–155} and can reduce development of severe retinopathy\textsuperscript{156}. Interestingly, in the Diabetes Prevention Program (DPP) restoring individuals to normal fasting and 2-hour glucose levels only once during the intervention phase was associated with a reduced rate of subsequently developing diabetes, due largely to improved β-cell function\textsuperscript{157}. 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?\textsuperscript{158} Only reports of the effects of
troglitazone in the DPP\textsuperscript{149} and glargine in ORIGIN\textsuperscript{123} suggest a residual benefit after prolonged withdrawal of the intervention. However, despite good rationale for approval of interventions to delay the onset of diabetes\textsuperscript{159}, no medication has yet received official sanction as a preventative treatment.

Finally, while type 2 diabetes largely affects adults, sadly it is now emerging in youth. The pathogenesis of the syndrome in children is also critically determined by β-cell function loss with the degree of residual β-cell function determining glucose control in recently diagnosed patients\textsuperscript{160}. The TODAY (Treatment Options for Type 2 Diabetes in Adolescents and Youth) study examined the impact of lifestyle and medications 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\textsuperscript{161}. The disease’s course in youth appears to be more aggressive than in adults, with the differential impact of the interventions being the result of a greater improvement in β-cell function\textsuperscript{160}. Further analyses from TODAY show that in youth with type 2 diabetes dyslipidaemia\textsuperscript{162} and hypertension\textsuperscript{163} are common and worsen over time. Both microalbuminuria and retinopathy increase with diabetes duration and severity is related to glycaemic control\textsuperscript{163,164}. These observations provide much needed insights and will certainly spawn additional work to allow us to better treat type 2 diabetes in youth. Hopefully we will find good alternatives as the very high morbidity in these young individuals has major implications for their quality of life as the duration of their disease lengthens and complications develop.

**What Does the Future Hold and Need?**

A number of the aforementioned studies are following participants for outcomes relevant to type 2 diabetes. In the DPP, conversion from impaired glucose tolerance to diabetes is known within six months of its occurrence and will allow a better understanding of the natural history of micro- and macrovascular complications and whether some of these, such as retinopathy, develop before the onset of diagnostic hyperglycaemia. In both DPP and Look AHEAD, assessment of the decline in longitudinal cognitive function will provide insight into this underappreciated deleterious outcome of hyperglycaemia. Passive follow up of ORIGIN, ADVANCE and TODAY participants will inform whether there is any beneficial legacy (“metabolic memory”) effect of improved glucose control on vascular disease, as was suggested initially in the follow up of patients with type 1 diabetes in the Diabetes Control and Complications Trial (DCCT/EDIC)\textsuperscript{165}, and subsequently in the follow up of the UKPDS\textsuperscript{166}. Given that improved glucose control reduces microvascular complications and greater progression of retinopathy is associated with increased cardiovascular disease\textsuperscript{167}, it is possible that a beneficial effect on cardiovascular outcomes may also be observed in these studies.

Cardiovascular safety of glucose-lowering medications has become an essential requirement for the registration of new medications\textsuperscript{168}, and large studies of incretin-based therapies (clinicaltrials.gov identifiers NCT00790205, NCT00968708, NCT01078886, NCT01144338, NCT01147250, NCT01179048, NCT01243424 and NCT01394952) and SGLT2 inhibitors (clinicaltrials.gov identifiers NCT01032629, NCT01131676 and
NCT01730534) are currently being undertaken. The results of SAVOR-TIMI 53 (NCT01107886) and EXAMINE (NCT00968708) were recently released and showed no increased risk of cardiovascular events with the DPP-4 inhibitors saxagliptin and alogliptin, respectively. Collectively, the studies examining GLP-1 receptor agonists and DPP-4 inhibitors will also provide an unbiased assessment of the possible increased risk of acute pancreatitis and malignant transformation in the pancreas with these agents. While 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 medication. One of these long-term studies directly compares a DPP-4 inhibitor to glimepiride (clinicaltrials.gov identifier NCT01243424) and will provide insight into whether there is an increased risk of cardiac events with sulphonylureas, a question lingering for over 40 years from the findings of the University Group Diabetes Program. Further, these studies should provide information on whether the incretin-based medications actually protect against cardiovascular disease, as suggested largely by meta-analyses of phase 2 and 3 studies. Finally, while 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? While current treatment algorithms are less prescriptive than before and advocate a more personalized approach to the choice of medications and treatment targets for type 2 diabetes, an important question that still remains is what medication to add after metformin? Current treatment algorithms are based largely on industry-conducted studies, which typically do not compare more than two medications and are short term. GRADE (Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study) will compare head-to-head for up to seven years of intervention the effect on metabolic control of the sulfonylurea glimepiride, the DPP-4 inhibitor sitagliptin, the GLP-1 analogue liraglutide, and the basal insulin glargine when added to metformin. It will also examine adverse effects, impact on cardiovascular risk factors, quality-of-life, tolerability and cost effectiveness as well as phenotypic characteristics associated with response to or failure of the four different medication combinations. The latter, along with genotyping of participants, should also provide insight into possible subtypes of the disease and a more accurate, pathogenesis-based approach to individualized treatment. However, GRADE will not address whether it is beneficial to initiate therapy with a combination of medications rather than the more traditional stepwise approach.

Given that current treatment approaches do not prevent or slow the loss of β-cell function, there is clearly an urgent need for alternative approaches. Restoring Insulin Secretion (RISE) is a feasibility study employing three different protocols to assess the effect on β-cell function of medical and surgical approaches in adults and children with impaired glucose tolerance or recently diagnosed diabetes. The medication protocols in adults and children will last 12 months with sophisticated insulin sensitivity and β-cell function testing at baseline, at the end of active treatment and after a 3-month washout. In adults, metformin alone, glargine followed by metformin, and liraglutide plus metformin will be compared to placebo (clinicaltrials.gov identifier NCT01779362), while in the children the former two regimens will be tested (clinicaltrials.gov identifier NCT01779375). The surgical protocol in
adults will compare on the same outcomes the impact of weight loss from laparoscopic banding to metformin alone over 24 months (clinicaltrials.gov identifier NCT01763346).

Surgical procedures aimed at reducing weight have been postulated to have benefits beyond simple weight loss and glucose control and include reduced cardiovascular events and mortality. However, these hypotheses are based on results from the Swedish Obese Subjects Study in which subjects were not randomized and the control group was contemporaneously matched, only received conventional treatment, and differed by a number of characteristics at baseline. Thus, there is a desperate need for appropriately controlled studies comparing surgical and non-surgical interventions to produce weight loss. Furthermore, long-term studies of the impact of “metabolic surgery”, which focuses primarily on correcting metabolic abnormalities rather than weight loss as does bariatric surgery, are required to determine whether the progression of diabetes can be slowed or halted and whether adverse events as a result of the surgery limit its utility. It would also be helpful to know the differential long-term positive and negative effects of simple restriction with banding versus the more complex bypass procedures.

Concluding Thoughts

When one reflects on where we are today, it is interesting that in 1984 Amsal and Marble wrote “Despite the availability of oral hypoglycaemic agents for nearly 30 years, their precise mode of action and role in the management of diabetes mellitus remains poorly defined and controversial.” Nearly thirty years after that statement, we still have a great deal to learn regarding the pathogenesis of type 2 diabetes and how best to use the therapies available to us, although clearly there has been great progress in elucidating their modes of action. One can only hope that the next 30 years will provide us with the knowledge and approaches that will allow us to limit the global harm of type 2 diabetes by not only managing the condition more effectively with a combination of non-pharmacological and pharmacological approaches, but also by preventing the disease and identifying new strategies to directly target its complications.

Search Strategy and Selection Criteria

We searched PubMed and Google Scholar primarily for original research articles published up to May 2013 that were focused on the pathophysiology and treatment of type 2 diabetes. The main search terms used were “pathophysiology”, “type 2 diabetes”, “prediabetes”, “β-cell”, “insulin resistance” and “treatment”. We identified primarily full-text manuscripts written in English. We also searched Clinicaltrials.gov for information on ongoing clinical trials in type 2 diabetes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.
Acknowledgments

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Conflicts of Interest

SEK has received honoraria for advisory work and lectures from Boehringer Ingelheim, Bristol-Myers Squibb, Elcelyx, 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 Astra Zeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Intarcia, Janssen, Merck Sharpe and Dohme, Novartis, Novo Nordisk, Roche Diagnostics, Sanofi aventis and Takeda as well as research support from Bristol-Myers Squibb, Merck Sharpe and Dohme, Novartis and Novo Nordisk.

References


_Lancet_. Author manuscript; available in PMC 2015 March 22.


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Figure 1.
Feedback loop between the islet β-cell and the insulin-sensitive tissues. (A) Insulin acts in the liver to suppress glucose production, and in the muscle and adipose tissue to stimulate the uptake of glucose, amino acids and fatty acids. The amount of insulin released to maintain normal glucose homeostasis is determined by the prevailing insulin sensitivity. This feedback is likely mediated through neuronal and humoral mechanisms, but the exact mediators are still not known. (B) When insulin resistance develops in the insulin-sensitive tissues, feedback to the β-cell ensures that it increases insulin output to maintain normal...
glucose tolerance. (C) When the β-cell is incapable of increasing insulin output in the presence of insulin resistance, the result is the development of elevated glucose levels, initially manifest as impaired glucose tolerance. As β-cell dysfunction progresses, further elevations in glycaemia occur and diabetes is the eventual result.
Figure 2.
Role of genes and the environment in the development of obesity and type 2 diabetes. The interaction of genes that influence body adiposity with environmental factors results in the development of obesity and its associated insulin resistance. However, only when genes for abnormal β-cell function are present along with those for body adiposity does the interaction with the environment result in the development of type 2 diabetes.
Figure 3.
(A) Timeline of the introduction of medications for treating type 2 diabetes. The rate of introduction of new classes of medications has accelerated over the last 20 years. The two classes indicated in red, animal insulin and inhaled insulin, are essentially no longer available as therapeutics. (B) Organ systems on which the different classes of medications have their primary mode of action. In the case of insulin, this is as replacement for this natural product of the islet β-cell. The classical organ systems are targets for which available and new interventions have been targeted for decades and comprise the pancreatic islet, liver, muscle and adipose tissue. The non-classical targets have been a focus more recently and include the intestine, kidney and brain.
Table 1
Oral and injectable medications currently approved for the treatment of hyperglycaemia in type 2 diabetes

<table>
<thead>
<tr>
<th>Oral Agents</th>
<th>Injectable Agents</th>
</tr>
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<tbody>
<tr>
<td><strong>Sulphonylureas</strong>&lt;br&gt;Second Generation</td>
<td><strong>Islet Amyloid Polypeptide (IAPP)/Amylin Analogues</strong>&lt;br&gt;• Pramlintide</td>
</tr>
<tr>
<td>• Glibenclamide/glyburide</td>
<td></td>
</tr>
<tr>
<td>• Gliclazide</td>
<td></td>
</tr>
<tr>
<td>• Glimepiride</td>
<td></td>
</tr>
<tr>
<td>• Glipizide</td>
<td></td>
</tr>
<tr>
<td><strong>Biguanides</strong>&lt;br&gt;</td>
<td><strong>GLP-1 Receptor Agonists</strong>&lt;br&gt;• Exenatide&lt;br&gt;• Liraglutide</td>
</tr>
<tr>
<td>• Metformin</td>
<td></td>
</tr>
<tr>
<td><strong>PPAR γ Agonists (Thiazolidinediones)</strong>&lt;br&gt;</td>
<td><strong>Insulin</strong>&lt;br&gt;Short Acting&lt;br&gt;• Regular insulin&lt;br&gt;• Insulin aspart&lt;br&gt;• Insulin glulisine&lt;br&gt;• Insulin lispro&lt;br&gt;• Prompt insulin zinc (Semilente)&lt;br&gt;Intermediate Acting&lt;br&gt;• Isophane insulin, neutral protamine Hagedorn (NPH)&lt;br&gt;• Insulin zinc (Lente)&lt;br&gt;Long Acting&lt;br&gt;• Extended insulin zinc (Ultralente)&lt;br&gt;• Insulin detemir&lt;br&gt;• Insulin glargine</td>
</tr>
<tr>
<td>• Pioglitazone</td>
<td></td>
</tr>
<tr>
<td>• Rosiglitazone</td>
<td></td>
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<tr>
<td><strong>α-Glucosidase Inhibitors</strong>&lt;br&gt;</td>
<td></td>
</tr>
<tr>
<td>• Acarbose</td>
<td></td>
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<tr>
<td>• Miglitol</td>
<td></td>
</tr>
<tr>
<td>• Voglibose</td>
<td></td>
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<tr>
<td><strong>Dipeptidyl Peptidase-4 (DPP-4) Inhibitors</strong>&lt;br&gt;</td>
<td></td>
</tr>
<tr>
<td>• Alogliptin</td>
<td></td>
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<tr>
<td>• Linagliptin</td>
<td></td>
</tr>
<tr>
<td>• Saxagliptin</td>
<td></td>
</tr>
<tr>
<td>• Sitagliptin</td>
<td></td>
</tr>
<tr>
<td>• Vildagliptin</td>
<td></td>
</tr>
<tr>
<td><strong>Sodium-Glucose Transporter-2 (SGLT2) Inhibitors</strong>&lt;br&gt;</td>
<td></td>
</tr>
<tr>
<td>• Canagliflozin</td>
<td></td>
</tr>
<tr>
<td>• Dapagliflozin</td>
<td></td>
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<tr>
<td>Oral Agents</td>
<td>Injectable Agents</td>
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<td>------------------------</td>
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<tr>
<td><strong>Glinides</strong></td>
<td></td>
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<tr>
<td>• Repaglinide</td>
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<tr>
<td>• Nateglinide</td>
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<tr>
<td><strong>Bile Acid Binding Resins</strong></td>
<td></td>
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<tr>
<td>• Colesevelam</td>
<td></td>
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<tr>
<td><strong>Dopamine Receptor Agonist</strong></td>
<td></td>
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<tr>
<td>• Bromocriptine</td>
<td></td>
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</tbody>
</table>

Note: Not all medications are available in all countries.
### Table 2
Selected therapeutic targets of largely untested mechanisms for type 2 diabetes

<table>
<thead>
<tr>
<th>Goal</th>
<th>Target</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase β-cell secretory function</td>
<td>A. GPR40 (FFAR1)</td>
<td>1 Activated by medium to long chain fatty acids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 TAK-875 first GPR40 agonist in Phase 3 clinical trials&lt;sup&gt;178&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>B. GPR119</td>
<td>1 Receptor located at β-cell and intestine, latter resulting in increased incretin hormone release&lt;sup&gt;179&lt;/sup&gt;</td>
</tr>
<tr>
<td>Increase β-cell mass</td>
<td>A. Liver-derived proteins, including betatrophin</td>
<td>1 Two recently discovered proteins increase β-cell mass in animal models&lt;sup&gt;180,181&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 Unclear whether targeting β-cell mass will adequately increase insulin production and secretion</td>
</tr>
<tr>
<td></td>
<td>B. FoxO1</td>
<td>1 Decreased FoxO1 results in β-cell dedifferentiation in mouse models, with some becoming α-cells&lt;sup&gt;182&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 Redifferentiation may result in cells capable of producing and secreting insulin</td>
</tr>
<tr>
<td>Decrease effect of glucagon</td>
<td>Glucagon receptor antagonists and glucagon antibodies</td>
<td>1 Block glucagon action lowers glucose&lt;sup&gt;144,145&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 Result in compensatory α-cell hyperplasia and increased plasma glucagon levels&lt;sup&gt;183&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 Associated with dyslipidemia</td>
</tr>
<tr>
<td></td>
<td>Oxynotomodulin</td>
<td>1 Product of the proglucagon gene</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 Agonist of both glucagon and GLP-1 receptors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 Induces weight loss in humans by reducing food intake and increasing energy expenditure&lt;sup&gt;184&lt;/sup&gt;</td>
</tr>
<tr>
<td>Reduce hepatic glucose production</td>
<td>A. Glucokinase</td>
<td>1 Aside from reducing glucose production, would also increase insulin secretion due to the critical role of the enzyme in the β-cell</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 Human studies show favourable effect on glucose lowering with increased hypoglycaemia. Glucose lowering effects not maintained beyond a couple of months&lt;sup&gt;185&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>B glucose-6-phosphatase</td>
<td>1 Goal is to decrease glycogenolysis and/or gluconeogenesis&lt;sup&gt;186&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>C fructose-1,6-bisphosphatase</td>
<td>2 Unwanted triglyceride accumulation in the liver&lt;sup&gt;186&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>D glycogen phosphorylase</td>
<td></td>
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<tr>
<td></td>
<td>E. CPT-1</td>
<td>1 Blocking CPT-1 inhibits fatty acid oxidation and selective inhibition in the liver should decrease gluconeogenesis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 Teglicar chronically reduces hepatic glucose production without changing peripheral glucose uptake, but increases hepatic triglyceride&lt;sup&gt;187&lt;/sup&gt;</td>
</tr>
<tr>
<td>Increase insulin action</td>
<td>A. AMPK</td>
<td>1 Chemical activators, examples of which include thienopyridone family, D-xylase and lipophilic</td>
</tr>
</tbody>
</table>

<sup>Lancet. Author manuscript; available in PMC 2015 March 22.</sup>
<table>
<thead>
<tr>
<th>Goal</th>
<th>Target</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-xylose derivatives, cilostazol, phytoestrogens, momordicosides, capsaicinoids, furanothiazolidine, AICAR</td>
<td></td>
<td>2 Structurally unrelated compounds, examples of which include chromium pibolinate, α-lipoic acid, kainic acid, cannabanoids, long chain fatty acids, reactive oxygen species, leptin, ghrelin, IL-6</td>
</tr>
</tbody>
</table>
| B. SIRT1                                                 |        | 1 Activation of SIRT1 downregulates the nuclear transcription factor p53, represses PPAR-γ; complexes with PGC-1α and HNF4α; increase insulin sensitivity and insulin secretion in rodents\(^{(188)}\)  
2 Caloric restriction specifically regulates tissue SIRT1 levels - increase in white adipose tissue, muscle, and pancreas; decrease in liver\(^{(188)}\)  
3 Prototype resveratrol, which is in grapes\(^{(189)}\) used to make wines  
4 Conflicting in vitro data whether SIRT1 will act as an oncogene or tumour suppressor\(^{(188)}\) |
| C. PTP1B                                                 |        | 1 Inhibition of PTP1B a potential treatment for type 2 diabetes and other insulin resistance-associated conditions  
2 Inhibition improves insulin sensitivity and reduces body weight, total cholesterol and triglycerides in high fat diet fed mice\(^{(189)}\) |
| D. FGF21                                                 |        | 1 Abundantly expressed in white adipose tissue, liver and pancreas\(^{(190)}\)  
2 In liver produces a profile similar to fasting by inducing gluconeogenesis, fatty acid oxidation and ketogenesis by inducing PGC-1α\(^{(190)}\)  
3 In humans FGF21 levels increase with prolonged fasting and are increased in overweight individuals with features of the metabolic syndrome\(^{(190)}\)  
4 Administration of a novel FGF21 variant to diabetic rhesus monkeys reduced body weight, glucose, insulin, LDL cholesterol, triglycerides and leptin while increasing HDL cholesterol and adiponectin\(^{(191)}\) |
| Decrease cellular inflammation                           | A. IKKβ/NF-κB pathway | 1 Studies in humans with type 2 diabetes using salsalate as an inhibitor reduced HbA1c by 0.37% over 48 weeks\(^{(192)}\)  
2 Urinary albumin excretion increases on therapy which reverses with withdrawal of treatment\(^{(192)}\) |
|                                                         | B. IL-1β receptor antagonists and IL-1β antibodies | 1 Primary target is intra-islet immune response resulting in IL-1β production\(^{(71)}\)  
2 Studies in humans have been mixed with modest effects to lower HbA1c\(^{(193)}\) |
| Reduce cortisol production                              | 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) | 1 Enzyme generates cortisol from its inactive form cortisone\(^{(194)}\)  
2 Enzyme implicated in visceral obesity and the metabolic syndrome\(^{(195)}\) with increased enzyme |

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<table>
<thead>
<tr>
<th>Goal</th>
<th>Target</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>activity in adipose tissue in obese and insulin resistant humans</td>
<td>196, 197</td>
<td>2 Inhibitors being developed for a variety of effects with glucose lowering thus far being modest</td>
</tr>
<tr>
<td>Co-agonist therapy</td>
<td>Glucagon and GLP-1</td>
<td>Principal is combining two peptides with different effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased energy expenditure with GLP-1 ameliorated the effects of glucagon to raise glucose</td>
</tr>
</tbody>
</table>

AMPK = AMP kinase; CPT-1 = carnitine palmitoyl-transferase 1; FFAR1 = free fatty acid receptor 1; FGF21 = fibroblast growth factor 21; GPR = G-protein coupled receptor; PGC-1α = peroxisome proliferator-activated receptor γ coactivator protein-1α; SIRT1 = sirtuin 1
Table 3
Results of intervention studies to prevent the development of type 2 diabetes in subjects with impaired glucose tolerance

<table>
<thead>
<tr>
<th>Study, Intervention and Citation</th>
<th>Number of Subjects Per Study Arm</th>
<th>Average Duration of Follow Up (years)</th>
<th>Incidence of Diabetes in Control/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>
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<tr>
<td>Da Qing</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Control</td>
<td>133</td>
<td>6.0</td>
<td>15.7</td>
<td></td>
<td></td>
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<tr>
<td>Diet</td>
<td>130</td>
<td></td>
<td>31</td>
<td>&lt;0.05</td>
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<tr>
<td>Exercise</td>
<td>141</td>
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<td>46</td>
<td>&lt;0.05</td>
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<tr>
<td>Diet and Exercise</td>
<td>126</td>
<td></td>
<td>42</td>
<td>&lt;0.05</td>
<td></td>
<td></td>
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<tr>
<td><strong>Finnish Diabetes Prevention Study</strong></td>
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<tr>
<td>Control</td>
<td>257</td>
<td>3.2</td>
<td>5.8</td>
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<tr>
<td>Lifestyle</td>
<td>265</td>
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<td>58</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td><strong>United States Diabetes Prevention Program</strong></td>
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<tr>
<td>Placebo</td>
<td>1082</td>
<td>2.8</td>
<td>11.0</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Lifestyle</td>
<td>1079</td>
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<td>58</td>
<td>&lt;0.001</td>
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<td><strong>Indian States Diabetes Prevention Programme</strong></td>
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<tr>
<td>Control</td>
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<td>2.5</td>
<td>18.3</td>
<td></td>
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<tr>
<td>Lifestyle</td>
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<td></td>
<td>28.5</td>
<td>0.018</td>
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<tr>
<td><strong>Medication</strong></td>
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<tr>
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</tr>
<tr>
<td>Placebo</td>
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<td>11.0</td>
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<td></td>
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<tr>
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Notes: Randomization by clinic and not by individual
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<th>Study, Intervention and Citation</th>
<th>Number of Subjects Per Study Arm</th>
<th>Average Duration of Follow Up (years)</th>
<th>Incidence of Diabetes in Control/Placebo Group (per 100 person years)</th>
<th>Relative Risk Reduction (%)</th>
<th>p value</th>
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Where 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.