Type 2 diabetes mellitus

Ralph A. DeFronzo[1], Ele Ferrannini[2], Leif Groop[3], Robert R. Henry[4], William H. Herman[5], Jens Juul Holst[6], Frank B. Hu[7], C. Ronald Kahn[8], Itamar Raz[9], Gerald I. Shulman[10], Donald C. Simonson[11], Marcia A. Testa[12] and Ram Weiss[13]

Abstract | Type 2 diabetes mellitus (T2DM) is an expanding global health problem, closely linked to the epidemic of obesity. Individuals with T2DM are at high risk for both microvascular complications (including retinopathy, nephropathy and neuropathy) and macrovascular complications (such as cardiovascular comorbidities), owing to hyperglycaemia and individual components of the insulin resistance (metabolic) syndrome. Environmental factors (for example, obesity, an unhealthy diet and physical inactivity) and genetic factors contribute to the multiple pathophysiological disturbances that are responsible for impaired glucose homeostasis in T2DM. Insulin resistance and impaired insulin secretion remain the core defects in T2DM, but at least six other pathophysiological abnormalities contribute to the dysregulation of glucose metabolism. The multiple pathogenetic disturbances present in T2DM dictate that multiple antidiabetic agents, used in combination, will be required to maintain normoglycaemia. The treatment must not only be effective and safe but also improve the quality of life. Several novel medications are in development, but the greatest need is for agents that enhance insulin sensitivity, halt the progressive pancreatic β-cell failure that is characteristic of T2DM and prevent or reverse the microvascular complications. For an illustrated summary of this Primer, visit: http://go.nature.com/V2eGfN

Correspondence to R.A.D.
e-mail: defronzo@uthscsa.edu
Diabetes Division, Department of Medicine, University of Texas Health Science Center, South Texas Veterans Health Care System and Texas Diabetes Institute, 701 S. Zarzamoro, San Antonio, Texas 78207, USA.

Article number: 15019
doi:10.1038/nrdp.2015.19
Published online
23 July 2015

Type 2 diabetes mellitus (T2DM) is characterized by dysregulation of carbohydrate, lipid and protein metabolism, and results from impaired insulin secretion, insulin resistance or a combination of both. Of the three major types of diabetes, T2DM is far more common (accounting for more than 90% of all cases) than either type 1 diabetes mellitus (T1DM) or gestational diabetes. Over the past few decades, our understanding of the development and progression of T2DM has evolved rapidly. Its main cause is progressively impaired insulin secretion by pancreatic β-cells, usually upon a background of pre-existing insulin resistance in skeletal muscle, liver and adipose tissue[1] (BOX 1). Overt hyperglycaemia is preceded by prediabetes[1,2], a high-risk condition that predisposes individuals to T2DM development (TABLE 1). Prediabetes is characterized by any one of the following: impaired fasting glucose (IFG) levels, impaired glucose tolerance (IGT) or increased glycated haemoglobin A1c (HbA1c) levels. Individuals with IFG levels are characterized by fasting plasma glucose levels that are higher than normal but do not meet the criteria for the diagnosis of diabetes. IGT is characterized by insulin resistance in muscle and impaired late (second-phase) insulin secretion after a meal, whereas individuals with IFG levels manifest hepatic insulin resistance and impaired early (first-phase) insulin secretion[2]. Individuals with prediabetes have HbA1c levels between 5.7–6.4%; they represent a heterogeneous group with respect to pathophysiology and are clinically very diverse. Annual conversion rates of prediabetes to T2DM range from 3% to 11% per year[3].

The clinical presentation, underlying pathophysiology and disease progression in patients with diabetes can vary considerably among individuals and, on occasion, atypical presentation of symptoms can make clear-cut classification of T2DM difficult. At the time of diagnosis, many patients with T2DM are asymptomatic, whereas others present with severe hyperglycaemia or even diabetic ketoacidosis. Latent autoimmune diabetes in adults[4] and maturity-onset diabetes of the young[5] can masquerade as T2DM. In asymptomatic individuals, the timing and frequency of testing for prediabetes or T2DM are based on the presence or absence of risk factors[6]. Screening in at-risk individuals is important because prediabetes is common and ~30% of individuals with T2DM are undiagnosed. Prevention of diabetes requires identification of individuals who have prediabetes and intervention with lifestyle modifications (weight loss and exercise) plus antidiabetic and anti-obesity medications[7–9]. The American Diabetes Association (ADA) Consensus Conference[10] recommended that high-risk individuals (HbA1c >6.5%; BMI ≥30 kg per m^2; age ≤60 years) with IGT or IFG levels be treated with metformin. Pioglitazone[11] and combined low-dose metformin and rosiglitazone[12]

Author addresses

[1]Diabetes Division, Department of Medicine, University of Texas Health Science Center, South Texas Veterans Health Care System and Texas Diabetes Institute, 701 S. Zarzamoro, San Antonio, Texas 78207, USA.
[2]CNR Institute of Clinical Physiology, Pisa, Italy.
[3]Department of Clinical Science Malmoe, Diabetes & Endocrinology, Lund University Diabetes Centre, Lund, Sweden.
[4]University of California, San Diego, Section of Diabetes, Endocrinology & Metabolism, Center for Metabolic Research, VA San Diego Healthcare System, San Diego, California, USA.
[5]University of Michigan, Ann Arbor, Michigan, USA.
[6]University of Copenhagen, Kobenhavn, Denmark.
[7]Department of Nutrition, Harvard T.H. Chan School of Public Health and Department of Epidemiology, Harvard T.H. Chan School of Public Health and Channing Division of Network Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA.
[8]Harvard Medical School and Joslin Diabetes Center, Boston, Massachusetts, USA.
[9]Diabetes Unit, Division of Internal Medicine, Hadassah Hebrew University Hospital, Jerusalem, Israel.
[10]Howard Hughes Medical Institute and the Departments of Internal Medicine and Cellular & Molecular Physiology, Yale University School of Medicine, New Haven, Connecticut, USA.
[11]Division of Endocrinology, Diabetes and Hypertension, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA.
[12]Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA.
[13]Department of Human Metabolism and Nutrition, Braun School of Public Health, Hebrew University, Jerusalem, Israel.

also are very effective in preventing the conversion of prediabetes to diabetes. Lifestyle intervention (weight loss and exercise) alone, although initially effective, is associated with weight regain in most individuals[13–15]. However, those individuals with prediabetes who successfully lose weight and maintain a physical activity programme can be expected to benefit from decreased conversion to diabetes[16], an improved lipid profile and reduced cardiovascular risk, including a reduced risk of developing hypertension.

T2DM is a complex chronic disorder that requires continuous medical care, patient self-management for control of abnormal glucose levels, and multifactorial risk reduction strategies to normalize blood glucose levels, lipid profiles and blood pressure to prevent or minimize acute and long-term microvascular complications (including retinopathy, nephropathy and neuropathy) and macrovascular complications (such as a heart attack and stroke)[17–19] (TABLE 2). T2DM should be viewed and treated as a heterogeneous disorder with multiple pathophysiological abnormalities, varying susceptibility to complications and varying clinical response to therapeutic intervention[17–19]. Ultimately, a true 'cure' for T2DM will require the elucidation of its molecular aetiology and effective interventions to combat the obesity epidemic. In this Primer, we discuss the epidemiology, diagnosis, pathophysiology and management (present and future) of T2DM.

Box 1 | **Glucose homeostasis**

Following a meal, insulin secretion is stimulated and glucagon secretion is inhibited by the combined actions of hyperinsulinaemia and hyperglycaemia. Approximately 60–70% of insulin secretion is dependent on the release of the incretin hormones, including glucagon-like peptide 1 (GLP1) and gastric inhibitory polypeptide (GIP) by the L cells and the K cells in the gut, respectively. Collectively, the changes in glucose, insulin and glucagon levels suppress hepatic glucose production, stimulate muscle glucose uptake and inhibit lipolysis; the latter results in a reduction in the free fatty acid concentration in blood, which further enhances the effect of insulin on the liver and muscle. Type 2 diabetes mellitus is associated with major disturbances in all of the preceding physiological responses: insulin secretion is impaired; fasting plasma glucagon levels are increased and fail to suppress normally after a meal; basal hepatic glucose production is increased and fails to suppress normally after a meal; muscle glucose uptake is impaired; fasting plasma free fatty acid levels are increased and fail to suppress normally following a meal; and the post-meal rise in GLP1 and GIP is normal or modestly decreased. However, there is severe β-cell resistance to the stimulatory effect of both GLP1 and GIP on insulin secretion.

Epidemiology

T2DM has become a major global public health concern (FIG. 1). The International Diabetes Federation estimated that, in 2013, 382 million adults aged 20–70 years worldwide had T2DM, with 80% of those affected living in low- and middle-income countries[20]. This number is expected to rise to 592 million by 2035 (REF. 20). Areas particularly affected by this disease are China and India, where the prevalence of T2DM has increased dramatically despite the relatively low prevalence of obesity[21]. Given the same body mass index (BMI), Asians tend to have a higher percentage of body fat mass, greater abdominal obesity and less muscle mass[22], which might explain their increased predisposition to T2DM. In addition, poor nutrition *in utero* and in early life, combined with overnutrition in later life, can contribute to the accelerated trajectory of the T2DM epidemic, especially in populations undergoing rapid nutrition transitions, involving changed food habits and reduced physical activity. Prevalence of T2DM is slightly higher in men than in women[20].

Epidemiological studies have improved our understanding of the behavioural, lifestyle and biological risk factors for T2DM (BOX 2). Increasing adiposity, as reflected by higher BMI levels, is the single most important risk factor for T2DM (FIG. 2). In addition, particular dietary components are associated with a reduced risk of T2DM, independent of body weight, including higher intake of whole grains, green leafy vegetables, nuts and coffee; lower intake of refined grains, red and processed meat, and sugar-sweetened beverages; and moderate intake of alcohol[23]. Physical inactivity is a key behavioural risk factor, and both aerobic activity and resistance training are beneficial[24]. Sedentary behaviour, such as prolonged television watching, is associated with increased risk[25]. Both short (≤5 hours per night) and long (≥9 hours per night) duration of sleep are associated with increased risk[26], as is rotating shift work[27]. In addition, cigarette smoking is a significant risk factor for developing T2DM, independent of body weight and other risk factors[21]. Although genetics play an important part in the development of T2DM[28], the ongoing diabetes epidemic cannot be explained by novel genetic mutations but is instead largely explained by the epidemic of obesity[29]. Nevertheless, genes determine how we respond to changes in the environment, and vice versa.

Table 1 | **Diagnostic reference values**

Parameters	Normal*	Prediabetes	T2DM
Haemoglobin A1c	<5.7%‡	5.7–6.4%‡	≥6.5%
	<6.0%§	6.0–6.4%§	
Fasting plasma glucose	<100 mg per dl‡	100–125 mg per dl‡	≥126 mg per dl
	<110 mg per dl§	110–125 mg per dl§	
Two-hour plasma OGTT	<140 mg per dl	140–199 mg per dl	≥200 mg per dl

OGTT, oral glucose tolerance test; T2DM, type 2 diabetes mellitus. *Normal glucose metabolism. ‡American Diabetes Association. §World Health Organization.

Our understanding of the pathophysiology of T2DM has been aided by the discovery of novel disease biomarkers. High blood concentrations of pro-inflammatory cytokines, such as C-reactive protein, interleukin-6 (IL-6) and tumour necrosis factor (TNF), are associated with an increased risk of T2DM[30], whereas a high concentration of adiponectin, which has anti-inflammatory effects, is associated with a reduced risk[31]. Lower levels of sex hormone-binding globulin are associated with increased risk[32], as are higher blood concentrations of branched-chain and aromatic amino acids[33]. Gut flora metabolites might predict future risk of T2DM because the gut microbiota is involved in energy extraction from the diet, modification of host gene expression, and increasing metabolic endotoxaemia (the level of endotoxins in blood) and chronic inflammation[34].

In summary, up to 90% of T2DM cases are potentially preventable by following a healthy diet, maintaining a BMI of ≤25 kg per m^2, exercising for at least 30 minutes per day, avoiding smoking and consuming alcohol in moderation[35,36].

Table 2 | **Multifactorial risk reduction outpatient goals of therapy in T2DM**

Parameter	ADA	AACE	IDF (WDF)
Glucose			
Fasting glucose (mg per dl)	70–130*	<110	115
2 hour postprandial glucose (mg per dl)	<180*	<140	<160
Haemoglobin A1c (%)	<7	≤6.5	<7.0
Lipids			
LDL cholesterol (mg per dl)	<70‡	70‡	<70‡
Non-HDL cholesterol (mg per dl)	NR	<130	<97
		<100‡	
HDL cholesterol (mg per dl)	>40 in men	>40 in men	>39
	>50 in women	>50 in women	
Triglycerides (mg per dl)	<150	<150	<200
Blood pressure			
Systolic pressure/diastolic pressure (mm Hg)	<140/80*	<130/80	≤130/80§

AACE, Association of Clinical Endocrinologists; ADA, American Diabetes Association; HDL, high-density lipoprotein; IDF, International Diabetes Federation; LDL, low-density lipoprotein; NR, no recommendation; T2DM, type 2 diabetes mellitus; WDF, World Diabetes Foundation. *Individualized goals. ‡High-risk or established cardiovascular disease. §Age 70–80 years goal <140/90 mmHg, and age >80 years goal <150/90 mmHg.

Mechanisms/pathophysiology

T2DM is a multifactorial disease involving genetic and environmental factors. The pathophysiological changes are characterized by β-cell dysfunction, insulin resistance and chronic inflammation, all of which progressively hamper control of blood glucose levels and lead to the development of micro- and macrovascular complications. With respect to hyperglycaemia, at least eight distinct pathophysiological abnormalities[1,37] contribute to impaired glucose homeostasis (FIG. 3), and these factors are already well established early in the natural history of T2DM. To the 'ominous octet' we can add two additional pathophysiological abnormalities: activation of inflammatory pathways and impaired insulin-mediated vasodilation, which both contribute to muscle insulin resistance.

Genetic factors

T2DM clusters in families and is heritable. The relative risk of siblings of a patient with T2DM developing the disease compared with families in which none of the siblings has the disease is ~2–3, but this figure increases to 30 if two siblings have T2DM[38]. The risk of developing T2DM is higher when the mother has the disease compared with when the father has the disease[39]. The risk of developing T2DM is also markedly increased with a BMI of ≥30 or a non-normal fasting glucose concentration of >5.5 mmol l^{-1} (REF. 40). By comparison, the relative risk for T1DM is ~15 and the relative risk for maturity-onset diabetes of the young is ~50. Identification of the genes that are responsible for complex polygenic diseases such as T2DM has been a challenge. A breakthrough came in 2007 with genome-wide association studies (GWASs) that reported common genetic variants associated with T2DM. A single-nucleotide polymorphism (SNP) in *TCF7L2* (already reported a year earlier on the basis of gene linkage analysis) showed the strongest association with T2DM[41,42], but SNPs in other genes have also been shown to be linked to T2DM, including in *SLC30A8*, *FTO*, *CDKAL1*, *CDKN2A*, *CDKN2B*, *HHEX*, *IGF2BP2*, *GCKR* and others[42–44]. Subsequent GWASs have increased this list to more than 100 common variants associated with T2DM[45]. Most variants are in introns, and it is more correct to talk about genetic loci than genes. Accordingly, defining the mechanisms by which these loci increase the risk of T2DM is difficult. Exceptions are a few variants in exons, which influence the function of the gene, such as *SLC30A8* (which encodes a zinc transporter that is required to store insulin)[46], *KCNJ11* (which encodes an ATP-dependent potassium channel) and *GCKR* (which encodes a glucokinase regulatory protein)[43–45]. Intronic variants might influence the expression of a nearby gene (in *cis*) or a distant gene (in *trans*), but this has been verified only for a small number of genes, such as a variant in the *MTNR1B* gene (which encodes a melatonin receptor)[47]. Cultured human islets carrying risk alleles have shown reduced β-cell function and survival. Gaining mechanistic insights into these SNPs has proved to be difficult, and animal data have not been very informative. For example, the human mutation in *SLC30A8* protects against T2DM, whereas it

predisposes to the disease in mice[46]. Other animal data have been more rewarding. Linkage to impaired insulin secretion in a polygenic model for T2DM, the GK rat, was explained by a variant in the *ADRA2A* gene, resulting in overexpression of the α2A-adrenergic receptor in islets[48]. As pretreatment of human islet cells with an inhibitor of the receptor, yohimbine, normalized insulin secretion, the authors treated human carriers of the variant with the same inhibitor, which resulted in a dose-dependent improvement in insulin secretion[49]. Impaired β-cell function has also been associated with epigenetic modifications[50] and microRNA patterns[51] that are likely to increase the fraction of cases in which inheritance is a relevant pathogenetic factor[42].

Notably, these genetic variants only have modest effects, increasing risk by 10–20%, and have thus been maintained during hundreds of generations. In fact, the majority of non-diabetic people carry risk variants for T2DM, and the average frequency of a T2DM-associated risk allele is 54%[45]. Despite this high prevalence and only modest risk increase, these variants have provided novel insights into the pathogenesis of T2DM. A prospective study of ~2,700 individuals, 150 of whom developed T2DM during 8 years of follow-up, tested the effect of a high genetic risk (highest quartile; ≥12 risk alleles) and low genetic risk (lowest quartile; ≤8 risk alleles) of T2DM and showed that all individuals became more obese and thereby insulin resistant regardless of high or low genetic risk. However, more high-risk people could not increase their insulin secretion to meet the demands imposed by insulin resistance and therefore developed T2DM[52].

The majority of heritability (85%) cannot be explained by the currently identified SNPs. Alternative possibilities to explain the heritability are: disease heterogeneity (T2DM may not be a genetically uniform disease), gene–environment interactions and epigenetic mechanisms (DNA methylation and chromatin modifications). Some variants, such as those for *KCNQ1* (which encodes a voltage-gated potassium channel), show strong parent-of-origin effects; *KCNQ1* is methylated and imprinted in fetal but not in adult life when inherited from the mother[53].

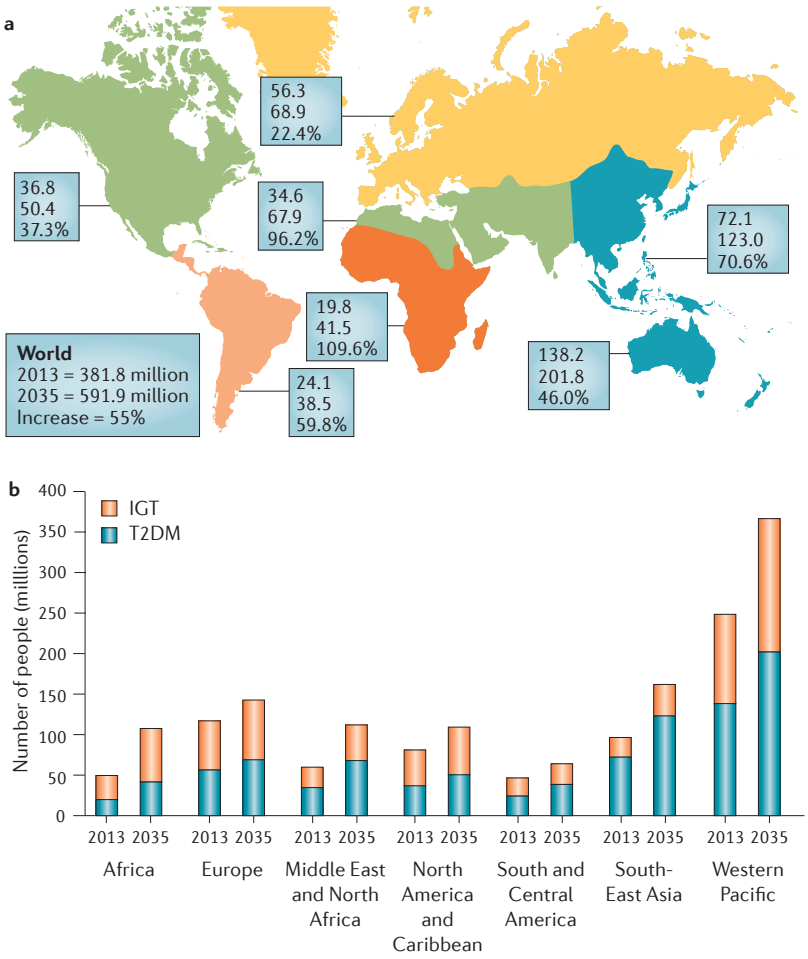

Figure 1 | **Prevalence of T2DM and IGT.** **a** | In each box, the top values are the number of people with type 2 diabetes mellitus (T2DM) (in millions) in 2013, and the middle numbers are an estimate of the number of people expected to have T2DM in 2035. The bottom value is the percentage increase from 2013 to 2035. **b** | The number of people with T2DM and impaired glucose tolerance (IGT) (in millions) by region for the years 2013 and 2035. Data are obtained from the International Diabetes Federation Diabetes Atlas.

β-cell function

Insulin resistance is the earliest detectable abnormality in individuals who are likely to develop T2DM[1,54,55]. However, overt T2DM does not occur unless β-cells are unable to secrete sufficient amounts of insulin to offset the insulin resistance[50,56,57]. Multiple factors contribute to β-cell failure, including ageing[58], genetic abnormalities[45], incretin hormone (glucagon-like peptide 1 (GLP1) and gastric inhibitory polypeptide (GIP)) resistance and/or deficiency[59,60], lipotoxicity[37,61,62], glucotoxicity[63], insulin resistance leading to β-cell stress[1,37], hypersecretion of islet amyloid polypeptide (IAPP)[64], reactive oxygen stress[65] and activation of inflammatory pathways[37].

β-cell physiology. In human islets, β-cells constitute ~60% of cells and are intermingled with glucagon-producing α-cells (30%), somatostatin-producing δ-cells (10%) and pancreatic polypeptide-producing cells (1%)[66]. Within the islet, β-cells form sparse subclusters, which show functional connectivity through gap junctions[67]. Each islet contains 100–500 μU of insulin, so that the whole endocrine pancreas (~1 million islets, weighing 0.9 g) contains 10 days' worth of supply for a healthy adult[68]. β-cells communicate with each other and with the other islet endocrine cells through connexin proteins and other cell–cell adhesion complexes[67]. Moreover, endocrine cells can influence one another via hormones released into the blood. Finally, non-hormonal endocrine cell products (such as ATP and zinc) and neurotransmitters influence β-cell function.

β-cells in T2DM. In post-mortem specimens from patients with T2DM, β-cell mass is reduced by 30–40% compared with specimens from non-diabetic subjects[69]. Morphometric measures, however, overlap widely between individuals with or without T2DM, and β-cell mass quantification based on insulin immunostaining

Box 2 | **Risk factors for T2DM**

- Older age
- Non-white ancestry
- Family history of type 2 diabetes mellitus (T2DM)
- Genetic factors
- Components of the metabolic syndrome (increased waist circumference, increased blood pressure, increased plasma triglyceride levels, and low plasma high-density lipoprotein (HDL) cholesterol levels and small dense low-density lipoprotein (LDL) cholesterol particles)
- Overweight or obese (body mass index (BMI) of ≥25 kg per m^2)
- Abdominal or central obesity (independent of BMI)
- Polycystic ovary syndrome
- History of atherosclerotic cardiovascular disease
- Unhealthy dietary factors (regular consumption of sugary beverages and red meats, and low consumption of whole grains and other fibre-rich foods)
- Cigarette smoking
- Sedentary lifestyle
- History of gestational diabetes or delivery of newborns >4 kg in weight
- Presence of acanthosis nigricans (hyperpigmentation of the skin)
- Some medications
- Short and long sleep duration and rotating shift work
- Psychosocial and economic factors

might lead to underestimation owing to β-cell degranulation[70]. Loss of β-cells in T2DM is believed to occur via apoptosis[71] and dysregulated autophagy[72]. β-cell proliferation does not seem to differ between diabetic and non-diabetic islets; whether neogenesis is impaired in T2DM is uncertain. Vascular disarray and amyloid deposition[73] contribute to altered cytoarchitecture in T2DM islets, especially in patients with long-standing disease. The quantitative functional impact of structural changes in human T2DM islets is still incompletely defined[73]. Insulin resistance feeds back to the β-cell by raising its set point (more insulin is secreted at any serum level of glucose). This chronic adaptation is probably mediated by small increments in circulating glucose levels (such as those that occur in obese normal glucose-tolerant individuals) as well as by other factors, such as raised levels of free fatty acids (FFAs)[74]. In addition, insulin resistance promotes a relative preponderance of α-cells over β-cells[74], possibly due to selective β-cell apoptosis as well as through a process of dedifferentiation and subsequent redifferentiation and to a progressive loss of β-cell mass. In culture, islets isolated from patients with T2DM show reduced insulin release in response to glucose and a higher threshold for the initiation of insulin secretion compared with islets isolated from healthy controls[75]. Similar changes in insulin secretion can be induced in islets isolated from non-diabetic individuals by prolonged exposure to increased concentrations of FFAs (in particular, palmitate)[76] or glucose[75], and *in vivo*[77].

Insulin secretion. β-cells integrate inputs from substrates (such as glucose, FFAs, arginine, fructose and amino acids), hormones and nerve endings to adjust insulin release in response to changing demands (for example, fasting–feeding cycles, exercise and stress) on a minute-to-minute basis in order to maintain normal blood glucose levels, and inter-individual differences affect this adjustment. For example, a lean, insulin-sensitive adult might need as little as 0.5 U of insulin to dispose of an oral load of 75 g of glucose over 2 hours, whereas an obese, insulin-resistant, glucose-intolerant person might require 45 U to perform the same task (~90-fold inter-individual difference). *In vivo* tests in humans using intravenous or oral glucose, arginine, sulfonylureas (antidiabetic drugs) or mixed meals have demonstrated impaired β-cell function in overt T2DM. However, reliable quantitation of *in vivo* β-cell dysfunction requires some form of modelling[78]. Absolute insulin secretion in response to an oral glucose challenge can be normal or even increased in T2DM (FIG. 4a), except in long-standing, poorly controlled disease, in which absolute insulin secretion is reduced. However, when insulin secretion rates are plotted against the concomitant plasma glucose concentrations, patients with T2DM secrete substantially less insulin than non-diabetic controls (FIG. 4b). This decline in β-cell glucose sensing occurs along a continuum extending from normoglycaemia through prediabetes to decompensated diabetes in adults[79] and children[80], and is a potent predictor of progression to diabetes independently of insulin resistance and classic phenotypic predictors[79]. Absolute insulin secretion is a positive antecedent of deteriorating glucose tolerance. Furthermore, the ability of β-cells to respond to the rate of increase in plasma glucose concentration (rate sensitivity) is impaired in individuals with T2DM[79].

Antecedent hyperglycaemia and high levels of incretin hormones (GLP1 and GIP) potentiate glucose-stimulated insulin release in healthy individuals. In patients with T2DM, glucose-mediated potentiation of insulin release is increased compared with normal glucose-tolerant individuals (owing to the hyperglycaemia); incretin potentiation, however, is severely compromised[81]. The incretin defect is not reversed by reducing the plasma glucose concentration[82].

Whenever an intervention results in a reduction in plasma glucose concentrations, fasting insulin secretion rate and total insulin output in response to glucose are reduced compared with the non-treated condition, but β-cell glucose sensitivity is improved. For example, successful bariatric surgery leads to partial recovery of β-cell function[83]. This indicates that a β-cell mass deficit alone is unlikely to be the cause of diabetes and that, even in advanced T2DM, many β-cells are alive but 'stunned' or 'disguised', and therefore amenable to being revitalized by intervention[84] (FIG. 5).

Insulin resistance

Obesity and physical inactivity lead to insulin resistance, which together with a genetic predisposition[45], place stress on β-cells, leading to a failure of β-cell function and a progressive decline in insulin secretion[1,2,7,57,85]. Insulin resistance precedes T2DM by many years[1,2,54,55]. Insulin resistance is not only present in muscle and the liver[1,84,85], the two tissues responsible for the majority of glucose disposal following carbohydrate

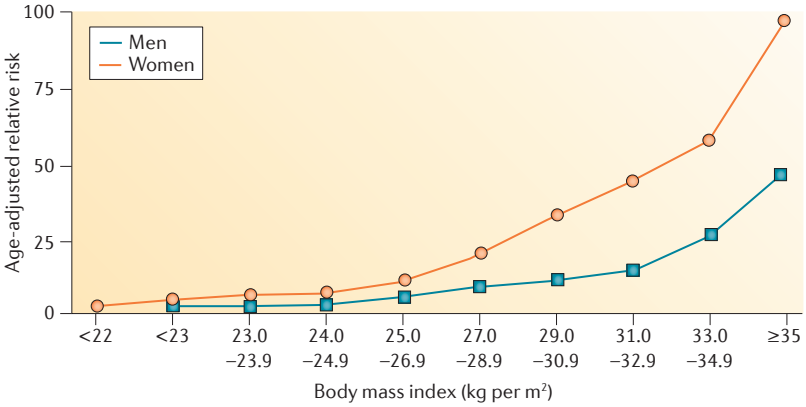

Figure 2 | **Association between BMI and T2DM.** Data obtained from REFS 321,322. BMI, body mass index; T2DM, type 2 diabetes mellitus.

ingestion, but also in adipose[86,87], kidney[88], gastrointestinal tract[89], vasculature[90] and brain[91,92] tissues, and pancreatic β-cells[93–95]. In muscle, multiple abnormalities contribute to insulin resistance, including defects in insulin signalling, glucose transport, glucose phosphorylation, glycogen synthesis, pyruvate dehydrogenase complex activity and mitochondrial oxidative activity[1,37,95]. In the liver, insulin resistance, together with insulin deficiency, hyperglucagonaemia, enhanced glucagon sensitivity and increased substrate (fatty acids, lactate, glycerol and amino acids) delivery[96–99], leads to increased gluconeogenesis, which is responsible for the increased basal rate of glucose production and fasting hyperglycaemia[1]. Also, insulin resistance in the kidney and augmented renal gluconeogenesis[88] contribute to fasting hyperglycaemia. Impaired suppression of hepatic glucose production, decreased hepatic glucose uptake, muscle insulin resistance, reduced non-insulin-mediated glucose uptake[100,101] and excessive renal glucose reabsorption[102] contribute to postprandial hyperglycaemia in T2DM. In addition, insulin resistance in the vascular endothelium impairs the vasodilating effects of insulin, thereby further reducing not only its own delivery but also glucose delivery[103,104].

Molecular mechanisms of insulin resistance. Binding of insulin to its receptor activates insulin receptor tyrosine kinase and phosphorylation of a family of insulin receptor substrates (IRSs), especially IRS1 and IRS2 (REF. 105) (FIG. 6). These phosphorylated IRS proteins bind to and activate intracellular signalling molecules, most important of which is phosphatidylinositol 3-kinase (PI3K). PI3K promotes glucose transporter type 4 (GLUT4) translocation to the plasma membrane, resulting in glucose uptake into skeletal muscle, and phosphorylates and inactivates the transcription factor forkhead box protein O1 (FOXO1), altering transcription of downstream genes. Insulin also stimulates the RAS–mitogen-activated protein kinase (MAPK) pathway.

Insulin resistance in obesity and T2DM has mainly been linked to the PI3K pathway[106,107]. Insulin resistance is usually associated with increased serine phosphorylation of IRS proteins, which inhibits tyrosine phosphorylation, leading to insulin resistance[108,109]. In some cases, serine phosphorylation also increases IRS degradation, further contributing to the insulin resistance[110]. The causes of increased serine phosphorylation are multifactorial, including ectopic lipid accumulation, mitochondrial dysfunction, inflammation and endoplasmic reticulum (ER) stress.

Ectopic lipids and PKCs. Ectopic lipid accumulation in muscle[37,111] and the liver[37,112–114] induces insulin resistance by increasing tissue diacylglycerol (DAG) levels[115], which lead to activation of members of a class of protein kinase C (PKC): PKCθ in muscle[107], and PKCδ[116] and PKCε[117] in the liver. These PKCs phosphorylate serine residues in IRS proteins, thereby inhibiting insulin signalling. Genetic knockdown of the genes encoding PKCθ in muscle[118], PKCδ[116] or PKCε[117] in the liver, or of the genes encoding one of the upstream enzymes involved in DAG production or accumulation[119] ameliorates lipid-induced insulin resistance. Consistent with this observation, the levels of PKCθ in muscle and of PKCδ and PKCε in the liver are increased in obesity and T2DM[116,120,121]. In addition, animal models of obesity and T2DM have increased tissue levels of ceramides, which are linked to insulin resistance[122]. Ceramides and DAGs might have different roles in promoting insulin resistance depending on the length of fatty acid chains[123] and sites of cellular compartmentalization[124]. Many treatments that improve insulin sensitivity, such as caloric restriction or thiazolidinediones, also reduce ectopic lipid content and tissue DAG content.

Mitochondrial dysfunction. Mitochondrial dysfunction has been observed in the liver, muscle, adipose tissue and even the brain, including and the hypothalamus, in rodents and humans with obesity, T2DM and metabolic syndrome[125]. The cause is both a reduction in mitochondrial density[119,126] and impaired mitochondrial functioning secondary to aberrant expression of different components of the oxidative phosphorylation system[127–129]. Altered mitochondrial function contributes to insulin resistance in multiple ways. In adipose tissue, mitochondrial dysfunction has been associated with impaired secretion of adiponectin, a potent insulin-sensitizing adipokine[127,130,131]. In other tissues, mitochondrial dysfunction has been suggested to increase levels of reactive oxygen species, which activate redox-sensitive serine kinases to phosphorylate IRS proteins and produce insulin resistance[132]. Whether mitochondrial dysfunction is the cause or result of insulin resistance remains a topic of debate[133]. However, given the key role of ectopic lipid deposition in causing insulin resistance, mitochondrial dysfunction associated with reduced mitochondrial fatty acid oxidation is at the very least an important exacerbating factor in this process[133].

Inflammation. Systemic inflammation is a well-documented contributor to insulin resistance. Increased levels of pro-inflammatory cytokines, such as IL-6 and TNF, and increased numbers of macrophages and other

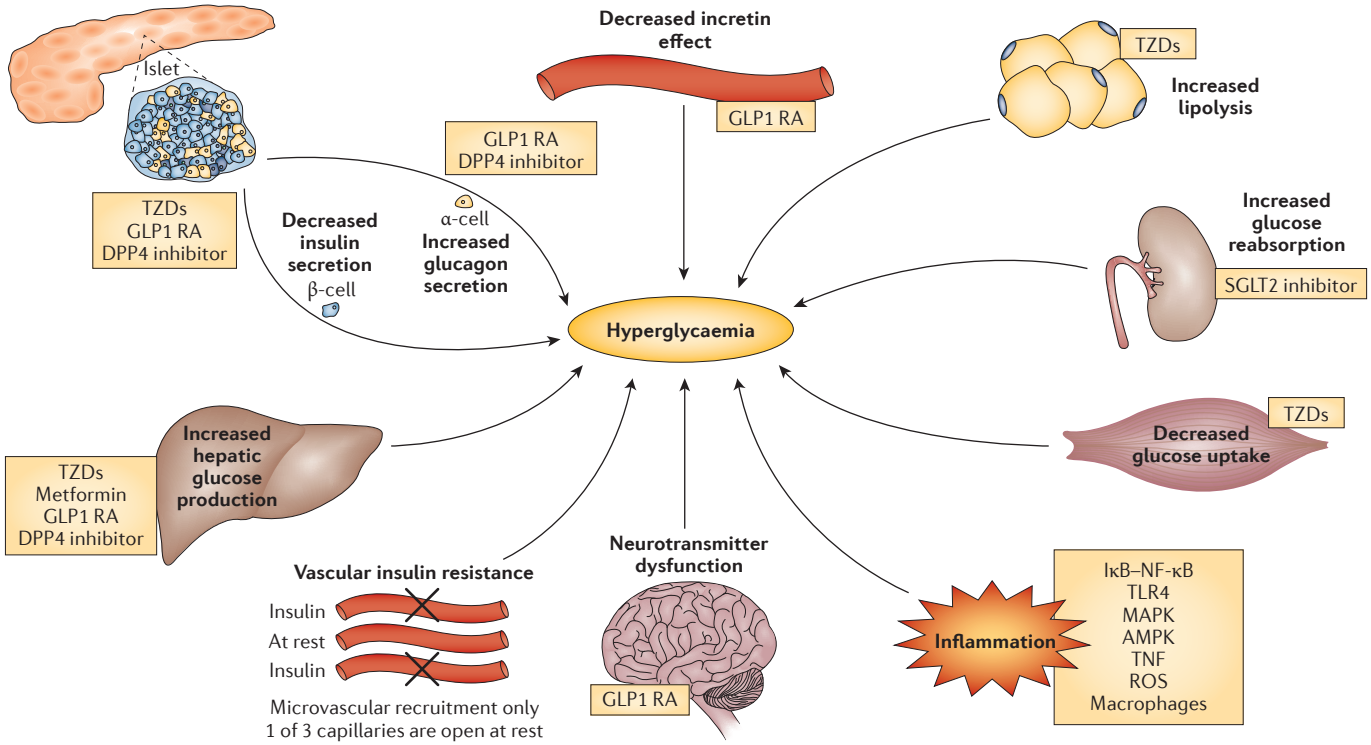

Figure 3 | **The 'ominous octet' of hyperglycaemia in T2DM.** Insulin resistance in muscle and the liver, and impaired insulin secretion by the pancreatic β-cells are the core defects in type 2 diabetes mellitus (T2DM). β-cell resistance to glucagon-like peptide 1 (GLP1) contributes to progressive failure in the function of β-cells, whereas increased glucagon levels and enhanced hepatic sensitivity to glucagon contribute to the excessive glucose production by the liver. Insulin resistance in adipocytes results in accelerated lipolysis and increased plasma free fatty acid (FFA) levels, both of which aggravate the insulin resistance in muscle and the liver and contribute to β-cell failure. Increased renal glucose reabsorption by the sodium/glucose co-transporter 2 (SGLT2) and the increased threshold for glucose spillage in the urine contribute to the maintenance of hyperglycaemia. Resistance to the appetite-suppressive effects of insulin, leptin, GLP1, amylin and peptide YY, as well as low brain dopamine and increased brain serotonin levels contribute to weight gain, which exacerbates the underlying resistance. To the 'ominous octet' must be added vascular insulin resistance and inflammation, making the 'decadent decoplet'. AMPK, AMP-activated protein kinase; DPP4, dipeptidyl peptidase 4; IκB, inhibitor of NF-κB; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; RA, receptor agonist; ROS, reactive oxygen species; TLR4, Toll-like receptor 4; TNF, tumour necrosis factor; TZDs, thiazolidinediones.

inflammatory cells are observed in adipose tissue, livers and sera of patients and animals in insulin-resistant states[134]. Pro-inflammatory cytokines induce insulin resistance by activating downstream kinases, including IκB kinase-β (IKKβ), JUN amino-terminal kinase 1 (JNK1; also known as MAPK8) and p38 MAPK, which can contribute to the phosphorylation of serine residues in IRS proteins[135,136] and stimulate production of suppressors of cytokine signalling (SOCS), which block the action of IRS proteins[137,138]. Blocking TNF activity with antibodies or knockout of its receptor improves insulin sensitivity in obese mice[139], but TNF-specific blocking agents do not improve glycaemic control in patients with T2DM[140]. Conversely, pharmacological and genetic inhibition of the IKKβ–nuclear factor-κB (NF-κB) pathway improves insulin sensitivity in mice[135,141,142] and improves glycaemic control in patients with T2DM[143], albeit modestly.

Macrophage infiltration in adipose tissue is a key aspect of insulin resistance[144] and is characterized by an increase in the numbers of pro-inflammatory M1 macrophages (classic macrophages) as well as T helper 1 (T_H1), T_H17 and $CD8^+$ T cells, and a reduction in the numbers of less-inflammatory cells, such as M2 macrophages, regulatory T cells (T_{Reg} cells) and T_H2 cells[145–147]. Inflammation occurs primarily in adipose tissue and the liver[142,148]. Macrophage infiltration in adipose tissue stimulates lipolysis, and increased levels of IL-6 can stimulate hepatic gluconeogenesis and cause hepatic insulin resistance[149]. Changes in adipose inflammation have been observed not only in obese mice but also in lean mice with differences in genetic predisposition to obesity and insulin resistance[150]. These inflammatory cells themselves are insulin responsive, and knockout of the insulin receptor in these lineages protects against obesity-induced inflammation and systemic insulin resistance[151].

Altered lipid metabolism can affect inflammation by activating Toll-like receptors (TLRs). Indeed, TLR4 is an important component of the innate immune response and is activated by fatty acids. Increased FFA levels can also increase the activity of IKK and JNK, cause serine phosphorylation of IRS proteins and block IRS tyrosine phosphorylation[152].

ER stress and the UPR. The ER is the major site of synthesis and folding of secreted and integral membrane proteins. States that increase protein synthesis or disrupt normal processing create an imbalance between the demand and capacity of the ER, leading to ER stress and the unfolded protein response (UPR). As a result, three signalling pathways are activated — IRE1α, PRKR-like ER kinase (PERK; also known as EIF2AK3) and ATF6α[153] — to reduce ER stress by ameliorating the UPR response. Pathophysiological states, including obesity, hyperlipidaemia and T2DM, disrupt this feedback loop by increasing phosphorylation of PERK and IRE1α, enhancing splicing of X box-binding protein 1 (XBP1) and activating JNK[154,155]. Conversely, weight loss[156] and administration of chemical chaperones that reduce ER stress[157] are associated with reduced UPR activation. Mechanistically, the UPR is thought to lead to insulin resistance through IRE1α-dependent activation of JNK[158]. Why ER stress develops in obesity is uncertain, but high fatty acid levels can cause ER stress and activate the UPR[159].

Another possible link between obesity and ER stress is the mammalian target of rapamycin (mTOR) signalling pathway. mTOR, which is involved in the regulation of a wide range of cellular functions, exists in two different complexes called mTORC1 and mTORC2 (REF. 160). Increased mTORC1 pathway activation blocks insulin signalling pathways by reducing insulin-induced tyrosine phosphorylation of IRS1 and IRS2 (REF. 161) and by increasing degradation of IRS1 (REF. 162). Recent studies have demonstrated that the p85α regulatory subunit of PI3K interacts with XBP1s (the spliced, transcriptionally active isoform of XBP1) and promotes the translocation of XBP1s into the nucleus to initiate the ER stress response[163].

Diabetic complications

Diabetic microvascular complications are closely related to the severity and duration of hyperglycaemia[164,165]. Hyperglycaemia promotes the development of microvascular complications through the activation of six major pathways, including enhanced polyol pathway flux, increased formation of advanced glycation end products (AGEs), increased AGE receptor expression, activation of PKC isoforms, enhanced hexosamine flux and increased intracellular reactive oxygen species[166,167]. Genetic factors have a pivotal role in determining susceptibility to microvascular complications. T2DM also affects the macrovasculature, and the incidence of myocardial infarction, peripheral vascular disease and stroke is markedly increased[37,168]. Reactive oxygen species impair angiogenesis, activate several pro-inflammatory pathways and cause epigenetic changes that result in long-lasting expression of pro-inflammatory genes that persists after glycaemia is normalized. These same biochemical and molecular mechanisms that contribute to the microvascular complications also contribute to the macrovascular complications[166,167].

Accelerated atherosclerotic cardiovascular disease is associated with several risk factors, including insulin resistance and hyperinsulinaemia, activation of inflammatory pathways and the presence of multiple cardiovascular risk factors (such as hypertriglyceridaemia, reduced high-density lipoprotein (HDL) cholesterol, small dense low-density lipoprotein (LDL) particles[169], hypertension, endothelial dysfunction, increased plasminogen activator inhibitor 1 levels, visceral obesity, and non-alcoholic steatohepatitis or non-alcoholic fatty liver disease)[37,170]. Hypertension is twofold–threefold more common in people with T2DM and greatly increases the risk of macrovascular complications

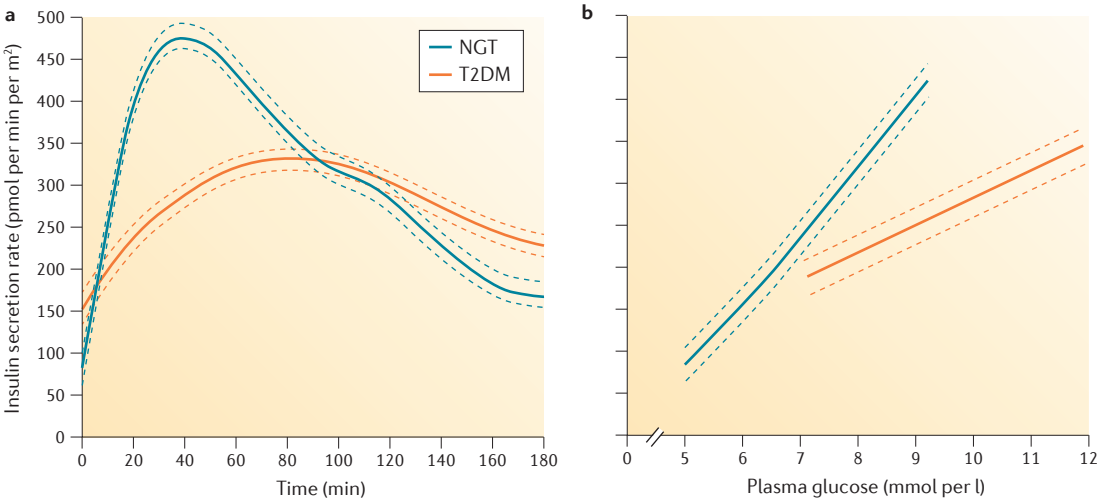

Figure 4 | **Insulin secretion in response to glucose.** **a** | Characteristic insulin secretory response (reconstructed by deconvolution of plasma C-peptide levels) to oral glucose in patients with type 2 diabetes mellitus (T2DM) and in body mass index (BMI)-matched non-diabetic individuals. Note the higher fasting secretion rate, the initial blunted secretory response and the later catch-up phase (due to higher glycaemia). **b** | The insulin secretion rates of panel **a** are here plotted against the concomitant plasma glucose concentrations to show the deficit in glucose sensing in patients versus normal glucose-tolerant (NGT) controls. Actual experimental data have been averaged and interpolated to produce these graphs.

(such as myocardial infarction, stroke, peripheral vascular disease and congestive heart failure), microvascular complications (including retinopathy and nephropathy) and premature death[171]. Multiple factors contribute to the increased incidence of hypertension in T2DM, including disturbed blood pressure circadian rhythms (higher nocturnal blood pressure), impaired blood flow autoregulation, stiffening of large arteries, increased intracellular sodium concentration, increased arterial sensitivity to angiotensin II, insulin resistance, endothelial dysfunction, obesity and genetic susceptibility[172,173].

Diagnosis, screening and prevention

Diagnosis

Diagnostic criteria for diabetes have traditionally relied on blood glucose levels. More recently, HbA1c has been added[174] as an integrated measure of long-term glycaemia (the lifespan of a red blood cell is ~120 days) (TABLE 1). However, haemolysis, which reduces red blood cell lifespan, can make HbA1c an invalid measure. Also, older age, non-white race, high dietary fat intake, alcohol consumption, cigarette smoking, liver disease, kidney disease and iron deficiency can affect HbA1c independently of glycaemia.

Although most clinicians agree that diabetes should be defined according to risk of complications, the level of hyperglycaemia associated with complications varies depending on the complication. Current criteria are based on maintaining fasting glucose, post-glucose-load glucose and HbA1c levels below the threshold that is associated with an increased risk of developing diabetic retinopathy[175].

T2DM diagnosis can be established on the basis of an elevated random plasma glucose test (≥200 mg per dl with classic symptoms of hyperglycaemia), fasting plasma glucose levels (≥126 mg per dl after at least an 8-hour fast), 2-hour post-glucose-load glucose level (≥200 mg per dl after 75 g oral glucose) or HbA1c (≥6.5%) confirmed by repeat testing unless unequivocally elevated[6] (TABLE 2). However, the risk of developing diabetic nephropathy and distal symmetric peripheral polyneuropathy is already increased with levels of hyperglycaemia lower than those associated with diabetic retinopathy[176]. In addition, the relationship between glycaemia and cardiovascular disease seems to be linear, without a clear threshold, which demonstrates the difficulty in using single cut points to diagnose a complex disease state[177].

Screening

Screening for a disease is appropriate if the disease is serious; its natural history is understood; it is detectable in its preclinical stage; the screening test is acceptable, quick, inexpensive and valid; early treatment is more effective than late treatment; and screening improves outcomes[178]. T2DM meets these criteria, and in 2014 the US Preventive Services Task Force (USPSTF) issued draft recommendations supporting screening for abnormal blood glucose levels and T2DM in adults[179]. Specifically, the USPSTF recommended that adults ≥45 years of age and those who are overweight or obese, or who have a first-degree relative with diabetes be screened in primary care settings. They also pointed out that most racial and ethnic minority groups (African Americans, Latinos and Hispanics) are at increased risk compared with whites. Other diabetes professional societies have long recommended opportunistic screening for T2DM within established primary care guidelines in high-risk individuals.

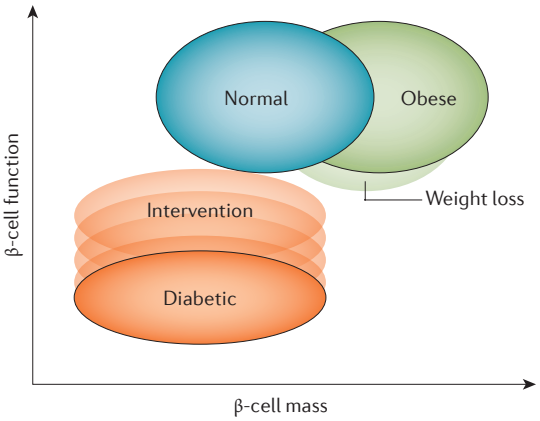

Figure 5 | **Schematic representation of the relationship between β-cell mass and β-cell function.** In obese individuals who are not diabetic, β-cell mass is expanded (in some proportion to the degree of weight excess), but β-cell function is comparable to individuals with a normal body mass index (BMI). Preliminary data show that weight loss might cause some reduction in both β-cell mass and function in non-diabetic individuals. Average β-cell mass is reduced in type 2 diabetes mellitus (T2DM) regardless of obesity, but the inter-individual variation is large. β-cell function, however, is profoundly impaired. Intervention, such as weight loss and/or antihyperglycaemic treatment, improves β-cell function but without changes in β-cell mass.

Fasting glucose, post-glucose-load glucose and HbA1c have limitations as screening tests that are related to their acceptability (fasting), time consumption (2-hour post-glucose-load glucose level) and cost (HbA1c). Some organizations have recommended the use of risk models and random capillary glucose levels as initial screening tests, but these have not been widely adopted[180,181]. In addition, different cut-off levels to define prediabetes have been proposed by international organizations[182] (TABLE 1). The use of lower thresholds to define increased risk of future diabetes improves sensitivity (that is, the probability of a positive screening test given that the individual is at high risk) but lowers specificity (that is, the probability of a negative screening test given that the patient is at low risk), and decreases the positive predictive value of the test (that is, the probability of being at risk given a positive screening test). The 2-hour post-glucose-load glucose level of 140–199 mg per dl (IGT) is the most-studied marker for future diabetes risk, and essentially all randomized clinical trials (RCTs) that have evaluated the efficacy of interventions for diabetes prevention have been performed in patients with IGT. Data supporting cut-off levels for fasting glucose and HbA1c that define prediabetes are more controversial and differ among organizations.

Prevention

RCTs have conclusively demonstrated that intensive lifestyle interventions and medications are effective in delaying or preventing the development of T2DM in high-risk individuals. The evidence base for these interventions is extensive and robust (TABLE 3). Four large randomized, controlled clinical trials demonstrated that diet and moderate physical activity designed to achieve and maintain 5–7% body weight loss reduce T2DM risk by 29–58%[16,183–185]. Lifestyle interventions are associated with improved quality of life (QOL) and are safe, cost-effective and effective across different ages, genders, and racial and ethnic groups, independent of the degree of obesity and hyperglycaemia. Metformin reduces the risk by 26–31%[184,185], α-glucosidase inhibitors (AGIs) reduce risk by 25–41%[186,187], and thiazolidinediones reduce risk by 55–72%[11,188,189]. Observational follow-up of RCT participants has demonstrated that the beneficial effects of lifestyle interventions may persist over time[190–192]. Efforts are underway to implement lifestyle interventions in primary care and community settings. Pharmacological interventions have been less widely applied, perhaps owing to the fact that no medication is approved by the US FDA for diabetes prevention.

Management

Management of T2DM is complicated by multiple pathophysiological disturbances[1,193] (FIG. 3) and the 'ABCDE' of diabetes management (Age, Body weight, Complications, Duration, Education and Expense, and Etiology)[19]. Prevention of microvascular complications focuses on glycaemic control[164–166], whereas prevention of macrovascular complications requires correction of classic cardiovascular risk factors that comprise the insulin resistance (metabolic) syndrome[37] (TABLE 3).

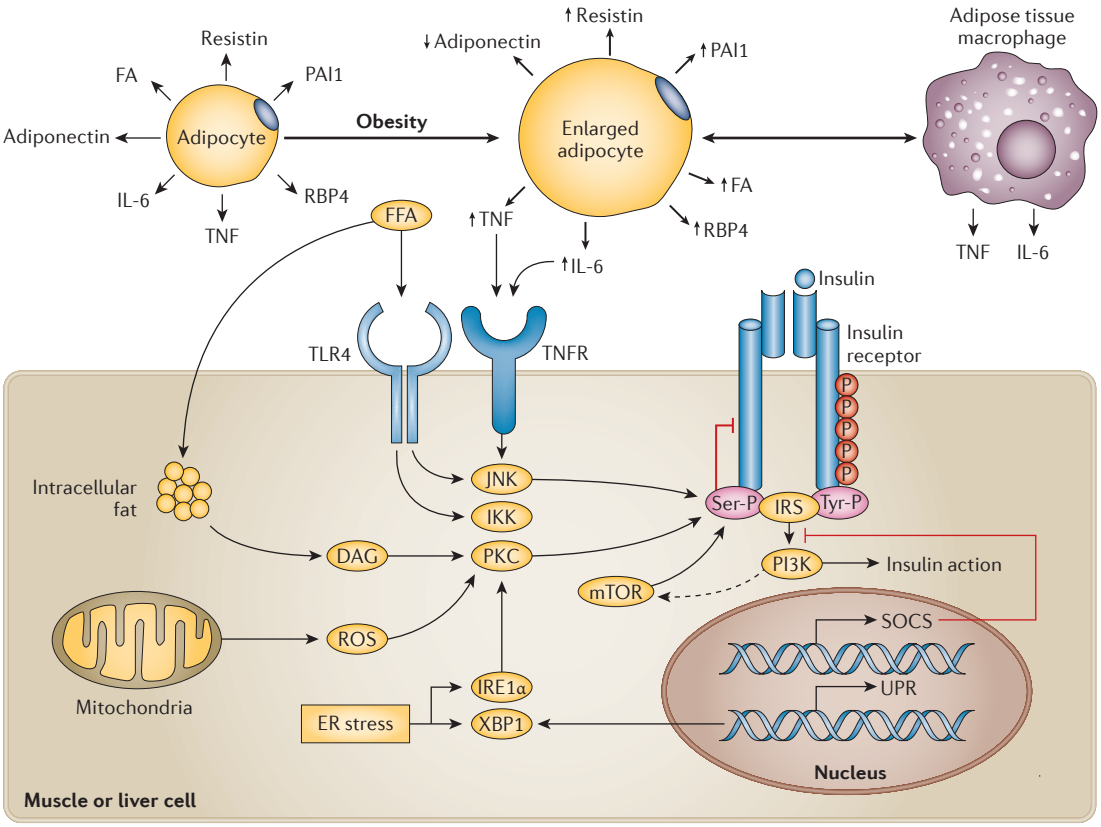

Figure 6 | **Mechanisms of insulin resistance.** In adipocytes, insulin resistance (also caused by increased insulin receptor substrate (IRS) serine phosphorylation) and inflammation lead to production and release of free fatty acids (FFAs) and insulin-resistance-provoking pro-inflammatory cytokines, such as interleukin-6 (IL-6), tumour necrosis factor (TNF) and resistin. Insulin-sensitizing adipokines, such as adiponectin, conversely, ameliorate insulin resistance. Also, retinol-binding protein 4 (RBP4) increases and might contribute to insulin resistance. Plasminogen activator inhibitor 1 (PAI1) does not affect insulin resistance but has been implicated in complications of obesity, including accelerated atherosclerosis and type 2 diabetes. These factors contribute to the accumulation of toxic lipid metabolites (diacylglycerol (DAG), ceramides and acyl-CoAs) in myocytes and hepatocytes, which impair insulin signalling (IRS–phosphatidylinositol 3-kinase (PI3K) pathway) and activate inflammatory pathways (JUN amino-terminal kinase (JNK), IκB kinase (IKK) and mitogen-activated protein kinase (MAPK)), which further impair the insulin signal transduction pathway. Mitochondrial dysfunction predisposing to DAG accumulation and nuclear protein kinase C (PKC) activation as well as generation of reactive oxygen species (ROS) and increased endoplasmic reticulum (ER) stress further exacerbate the insulin resistance[95,125]. FA, fatty acid; mTOR, mammalian target of rapamycin; SOCS, suppressors of cytokine signalling; TLR4, Toll-like receptor 4; TNFR, TNF receptor; UPR, unfolded protein response; XBP1, X box-binding protein 1.

Table 3 | **Intervention to delay or prevent T2DM development***

Intervention	Risk reduction (%)	Refs
Lifestyle (body weight reduction of 5–7%)	29–58	183–185
Metformin	26–31	184,185
Lifestyle and metformin	28	185
Acarbose (α-glucosidase inhibitor)	25	186
Voglibose (α-glucosidase inhibitor)	41	187
Troglitazone	55	188
Rosiglitazone	60	189
Pioglitazone	72	11

T2DM, type 2 diabetes mellitus. *In people with impaired glucose tolerance.

Ideally, HbA1c should be reduced to as close to normal without causing adverse effects, of which hypoglycaemia is the greatest concern[16,17,19,193,194]. Patients with T2DM with HbA1c levels persistently <6.5% do not develop retinopathy[195]. Because obesity and physical inactivity are insulin-resistant states associated with tissue fat overload (lipotoxicity)[37,61], lifestyle modification should be a basic component of all intervention programmes[16,17]. However, despite initial weight loss, most patients regain lost weight over the subsequent 1–2 years[13–15]. Further, despite successful weight loss, ~50% of obese individuals with prediabetes still progress to overt diabetes[192]. Thus, most obesity experts recommend concomitant anti-obesity medications to help to promote and maintain weight loss. Mobilization of fat from the liver and muscle, and β-cells improves hepatic and muscle insulin sensitivity and β-cell function[37,196,197].

Antidiabetic medications

Achievement of durable glycaemic control requires antidiabetic medications that reverse the pathophysiological defects that are present in T2DM[1,198]. Because no single medication reverses the multiple abnormalities, combination therapy has gained widespread acceptance and will continue to grow[1,198–201]. Normalization of HbA1c at the time of diagnosis results in improved long-term glycaemic control[7,8,200,202,203]. For prediabetes, pharmacological therapy with thiazolidinediones[11,204], GLP1 receptor agonists[205], metformin[192] and AGIs[186] effectively prevents or delays the progression of IGT to diabetes (TABLE 4).

Metformin. Metformin is the most commonly prescribed antidiabetic medication worldwide and works by suppressing hepatic glucose production, leading to a reduction in fasting plasma glucose levels and HbA1c[206]. Metformin has no effect on β-cell function[206,207] and, in the absence of weight loss, does not improve muscle insulin sensitivity[206]; thus, after an initial decrease, HbA1c rises progressively[207–209]. The mechanisms by which metformin suppresses hepatic glucose production remain unclear but include inhibition of mitochondrial complex I, activation of AMP-activated protein kinase (AMPK), and inhibition of glycolytic and/or gluconeogenic enzymes and mitochondrial glycerophosphate dehydrogenase[210,211]. In a study carried out in the United Kingdom and United States, cardiovascular events were significantly reduced in a small group of 344 obese patients with diabetes who were treated with metformin[212].

Drugs that increase insulin secretion. Sulfonylureas augment insulin secretion, and the resulting hyperinsulinaemia overcomes insulin resistance, leading to a decline in fasting plasma glucose levels and HbA1c. However, after the initial decline, HbA1c rises progressively because sulfonylureas have no long-term protective effect on β-cell function[1,207,209] and might even accelerate failure of β-cell function[213]. Sulfonylureas commonly cause hypoglycaemia and are associated with weight gain, and some retrospective studies suggest that they might increase cardiovascular events[214,215]. Compared with glibenclamide, the short-acting sulfonylurea, gliclazide has been associated with a reduced risk of all-cause mortality and cardiovascular death and is less likely to cause weight gain and hypoglycaemia[216]. Stepwise addition of sulfonylurea to metformin, or vice versa, is associated with progressive failure of β-cell function and rise in HbA1c[217]. However, because they are inexpensive, metformin and sulfonylureas remain the most commonly prescribed oral antidiabetic agents worldwide.

Meglitinides (repaglinide and nateglinide) are short-acting insulin secretagogues that require administration before each meal. Although related with less hypoglycaemia than sulfonylureas, they do not prevent the progressive decline in β-cell function and rise in HbA1c that is associated with T2DM.

Insulin sensitizers. Thiazolidinediones (pioglitazone and rosiglitazone) are the only true insulin-sensitizing agents[1,37,217,218]. They enhance insulin action in skeletal and cardiac muscle, the liver and adipocytes[1,37,217–219], and exert a potent effect on β-cells to augment and preserve insulin secretion[220–222]. Multiple mechanisms mediate their insulin-sensitizing effects: increased insulin signalling; stimulation of several intracellular steps involved in glucose metabolism (GLUT4, glycogen synthase and pyruvate dehydrogenase); stimulation of peroxisome proliferator-activated receptor-γ (PPARγ); PPARγ coactivator 1 (PGC1) activation leading to increased fat oxidation; proliferation of subcutaneous adipocytes and activation of genes involved in lipogenesis; fat redistribution from visceral to subcutaneous stores; reduced plasma levels of FFAs; a reduction in circulating inflammatory cytokines; and an increase in adiponectin levels[1,61,217,218]. The combined insulin-sensitizing and β-cell stimulatory effects of thiazolidinediones explain their durable action, which was shown to be up to 5 years in the ADOPT study, and their ability to reduce HbA1c[209,221,222]. Pioglitazone favourably affects many components of insulin resistance (metabolic) syndrome[217,218] and reduced the MACE end points (myocardial infarction, stroke and cardiovascular death) in the PROactive study[223]. Adverse events (including fluid retention, fat mass gain and trauma-related fractures in post-menopausal women) are dose related, and doses >30 mg per day should be avoided[224]. Weight gain

is common with thiazolidinediones, but the greater the weight gain, the greater the decrease in HbA1c and the greater the improvements in insulin sensitivity and β-cell function[220,221]. Concerns about the link between bladder cancer and pioglitazone have been dispelled by a 6-year follow-up in the PROactive study[225] and a recently completed 10-year US FDA-mandated study[226]. In a review of approximately one million people from six populations, no increase in bladder cancer was observed with either pioglitazone (hazard ratio: 1.01–1.04) or rosiglitazone (hazard ratio: 1.00–1.01)[227].

GLP1 modulators. T2DM is associated with severe GLP1 resistance in β-cells[60,228,229]. Dipeptidyl peptidase 4 (DPP4) inhibitors (sitagliptin, saxagliptin, linagliptin, alogliptin and vildagliptin) prolong the half-life of endogenously secreted GLP1. As DPP4 inhibitors do not increase (only prolong) plasma GLP1 levels, their ability to augment insulin secretion and reduce HbA1c is modest[230,231]. Their primary effect to improve glycaemic control is mediated by inhibition of glucagon secretion and reduction in basal hepatic glucose production[232]. DPP4 inhibitors have an excellent safety profile[233]. Concerns about pancreatitis have not been substantiated in prospective trials[233]. Two large cardiovascular outcome studies have demonstrated a hazard ratio of 1.0 for the primary end point (MACE) for both alogliptin[234] and saxagliptin[235], although a 27% increase in the incidence of hospitalization for congestive heart failure was observed with saxagliptin compared with placebo. The results of TECOS (sitagliptin) and ELIXIR (lixisenatide) presented at the ADA National Science Meeting (2015) also showed a hazard ratio of ~1.0 for the primary cardiovascular end point. Many cardiovascular outcome trials with the newer antidiabetic agents are ongoing, and results will be reported during the next 2–3 years.

GLP1 receptor agonists (exenatide, liraglutide, albiglutide, lixisenatide and dulaglutide) cause a pharmacological increase in plasma GLP1 levels, markedly augment insulin secretion and inhibit glucagon secretion[236,237]. The increase in the levels of plasma insulin and the decrease in those of glucagon effectively suppress hepatic glucose production[236] and cause a durable reduction — for up to 3 years — in HbA1c[237,238]. GLP1 receptor agonists promote weight loss (resulting in improved insulin sensitivity), delay gastric emptying (which is accelerated in patients with new-onset diabetes), correct endothelial dysfunction, reduce blood pressure, improve the plasma lipid profile and reduce C-reactive protein levels[238,239]. Combination therapy with a GLP1 receptor agonist plus basal insulin has been shown to be very effective in reducing HbA1c while preventing the weight gain associated with insulin therapy, without an increased risk of hypoglycaemia[240]. Nausea and vomiting are the most common side effects with GLP1 receptor agonists, but these are usually mild and dissipate within 4–8 weeks. An increased incidence of pancreatitis has not been observed in large healthcare databases[234,235,241].

Targeting intestinal and renal glucose absorption. AGIs (acarbose and voglibose) slow the rate of carbohydrate absorption in the intestine and increase meal-stimulated GLP1 secretion. The HbA1c-lowering effect of AGIs is modest and comparable to the effect of DPP4 inhibitors. In a review of 41 RCTs in the Cochrane Database[242], AGIs reduced HbA1c by 0.8%, which is similar to the HbA1c-lowering effect of gliptins (0.7–0.8%) in two different meta-analyses[243,244]. However, AGIs have been shown to decrease the conversion of prediabetes to diabetes in the STOP NIDDM trial[186]. Adverse effects of AGIs are related to the gastrointestinal tract (diarrhoea, abdominal pain, nausea and vomiting).

Table 4 | **Characteristics of major classes of currently available antidiabetic agents**

Drugs	Glycaemic efficacy (HbA1c)	Durability	Mechanism of action	Body weight	CV risk factors	CV safety	Side effects
Metformin	↓↓	No	↓↓ HGP	↓	↓	Possibly beneficial[212]	GI and lactic acidosis
Sulfonylureas	↓↓	No	↑↑ Insulin secretion	↑	Neutral	Possibly detrimental[214,216]	Hypoglycaemia
TZDs (pioglitazone)	↓↓	Yes	↑↑ Insulin sensitivity ↑↑ β-cell function	↑↑*	↓↓	Probably beneficial[223]	Fluid retention Bone fractures
DPP4 inhibitors	↓	No	↓ Glucagon secretion ↑ Insulin secretion (weak)	Neutral	Neutral	Neutral[234,235]	None
SGLT2 inhibitors	↓↓	Not known	↓↓ Glucosuria ↓↓ Glucotoxicity	↓	↓	Unknown	Genital mycotic infections Volume-related
AGIs	↓	Not known	↓ Carbohydrate absorption	Neutral	Neutral	Possibly beneficial[186]	GI
GLP1 receptor agonists	↓↓	Yes	↑↑ Insulin secretion ↓↓ Glucagon secretion	↓↓	↓↓	Not known	Nausea and vomiting
Insulin	↓↓	Yes‡	↓ HGP ↑ Glucose uptake in muscle	↑↑	Neutral	Neutral[257]	Hypoglycaemia

↓, decreased; ↑, increased; AGIs, α-glucosidase inhibitors; CV, cardiovascular; DPP4, dipeptidyl peptidase 4; GI, gastrointestinal; GLP1, glucagon-like peptide 1; HbA1c, haemoglobin A1c; HGP, hepatic glucose production; SGLT2, sodium/glucose co-transporter 2; TZDs, thiazolidinediones. *The greater the weight gain, the greater the improvements in insulin secretion and insulin sensitivity. ‡Requires increasing insulin dose. The number of arrows defines severity.

Sodium/glucose co-transporter 2 (SGLT2) inhibitors (dapagliflozin, canagliflozin and empagliflozin) block glucose absorption in the proximal renal tubule[245,246]. They decrease the maximum renal glucose reabsorptive capacity and, importantly, reduce the blood glucose threshold (to <40 mg per dl) at which glucose spills into the urine[102]. The increased glucose removal from the body via glucosuria leads to a reduction in plasma glucose, which results in the amelioration of glucotoxicity, with improved β-cell function and enhanced insulin sensitivity as a consequence[247,248]. Their glucose-lowering efficacy is equivalent to that of metformin, and loss of calories in urine (4 calories per gram glucose) promotes weight loss of ~2.5–3.0 kg[245]. Because SGLT2 inhibitors also suppress sodium transport, they cause mild extracellular volume depletion and reduce blood pressure (~5–6 mmHg in systolic pressure and ~1–2 mmHg in diastolic pressure). Their glucose-lowering efficacy is offset by: increased glucose absorption by SGLT1, which can reabsorb ~30–40% of filtered glucose following SGLT2 blockade[249], and 'paradoxical' stimulation of endogenous glucose production associated with increased glucagon and reduced insulin secretion[247,248]. SGLT2 inhibitors can be combined with all antidiabetic medications, including insulin. The efficacy of SGLT2 inhibitors is reduced when the estimated glomerular filtration rate declines to <45–60 ml per min per 1.73m^2. Adverse effects include genital mycotic infections in female patients, balanitis in uncircumcized male patients, urinary tract infections and volume-related side effects in older patients and individuals taking diuretics. Recently, cases of euglycaemic ketoacidosis have been described with SGLT2 inhibitors, primarily in T1DM, but also in T2DM. The potential of SGLT2 inhibitors to prevent diabetic nephropathy is being studied[250]. Combined SGLT2 and SGLT1 inhibitor therapy has considerable appeal. When SGLT2 is blocked, modest inhibition (~30%) of SGLT1 can increase glucosuria by ~80%[249]. Furthermore, 30% inhibition of gut SGLT1 produces an acarbose-like effect, which further reduces HbA1c by 0.5–0.6%[249].

Adding insulin. If oral or injectable antidiabetic agents fail to normalize HbA1c, patients with T2DM can be treated with insulin, but large doses (>80–100 units per day) are often required[251]. Combining insulin therapy with thiazolidinediones or metformin can improve glycaemic control and enable insulin dose reduction. The combination of GLP1 receptor agonists with basal insulin therapy causes robust HbA1c reduction, while reducing insulin dose and promoting weight loss[252]. Combining SGLT2 inhibitors with insulin also effectively reduces HbA1c, decreases insulin dose, promotes weight loss and reduces hypoglycaemia[253]. In new-onset T2DM, intensive insulin therapy[202,203] to reverse the metabolic decompensation, such as glucotoxicity and lipotoxicity, has proved effective in maintaining glycaemic control (HbA1c ~6.0%) for long periods.

Hypoglycaemia

Hypoglycaemia is a potential adverse effect of all antidiabetic agents, especially insulin secretagogues (sulfonylureas) and insulin[254,255]. According to the ADA, hypoglycaemia is defined as a plasma glucose level of <70 mg per dl. Most cases are mild, but severe hypoglycaemia (requiring third-party assistance for recovery) has been reported in 5–10% or more of individuals treated with sulfonylureas and insulin. Hypoglycaemia has been associated with myocardial infarction, ventricular arrhythmias, stroke and weight gain[254–256]. In the ACCORD study, the incidence of severe hypoglycaemia and weight gain was 3.1% and 3.5%, respectively, in the intensively treated group, and the study was stopped early because of an increased incidence of sudden death[257]. Risk factors for hypoglycaemia include use of insulin or sulfonylureas, missed meals, strenuous exercise, alcohol consumption, interaction with other drugs, advanced age and renal or hepatic disease.

Cardiovascular comorbidities

Controversy has arisen about the optimal treatment goal for hypertension in T2DM based on results of the ACCORD trial[258], which reported that targeting a systolic blood pressure of <120 mmHg did not reduce the composite primary outcome of cardiovascular events and was associated with more adverse events. This led to a reappraisal of optimal blood pressure levels to a less-stringent target of 140/90 mmHg[259]. However, in ACCORD, patients targeted to a systolic blood pressure of <120 mmHg experienced 40% fewer strokes[258], and a meta-analysis of 40 RCTs (n = 100,354 participants) reported that a 10 mmHg decrease in systolic blood pressure was associated with a relative risk reduction (RRR) of 27% for stroke, 13% RRR for death, 12% RRR for coronary heart disease events, 13% RRR for retinopathy and 17% RRR for albuminuria[260]. Hyperglycaemia is a relatively weak risk factor for cardiovascular disease in T2DM[164], and the anti-atherogenic effect of HbA1c reduction might take >10 years to manifest[165]. Dyslipidaemia is a major risk factor for cardiovascular disease in T2DM, and hypercholesterolaemia should be treated aggressively (TABLE 2).

Quality of life

T2DM imposes a substantial physical and psychological burden on patients, resulting in reduced health status and QOL. The relationship between improvements in HbA1c, reduced symptoms of hypoglycaemia and hyperglycaemia, and enhanced QOL was clearly demonstrated more than 15 years ago[261]. Since then, many classes of glucose-lowering medications and different types of insulin have been approved, but few comparative-effectiveness studies exist to guide treatment choices on the basis of patient-centred outcomes such as QOL[262].

The complexity, burden and adverse effects of diabetes therapies reduce QOL, satisfaction and adherence to therapy, often leading to suboptimal glycaemic control. However, comparative longitudinal studies assessing patient-centred outcomes are relatively rare. Moreover, when they are used, assessments often lack the measurement properties such as sensitivity, responsiveness and ability to detect changes that are meaningful to patients[263]. As the number of approved diabetes treatments increases, therapeutic decisions will be made on

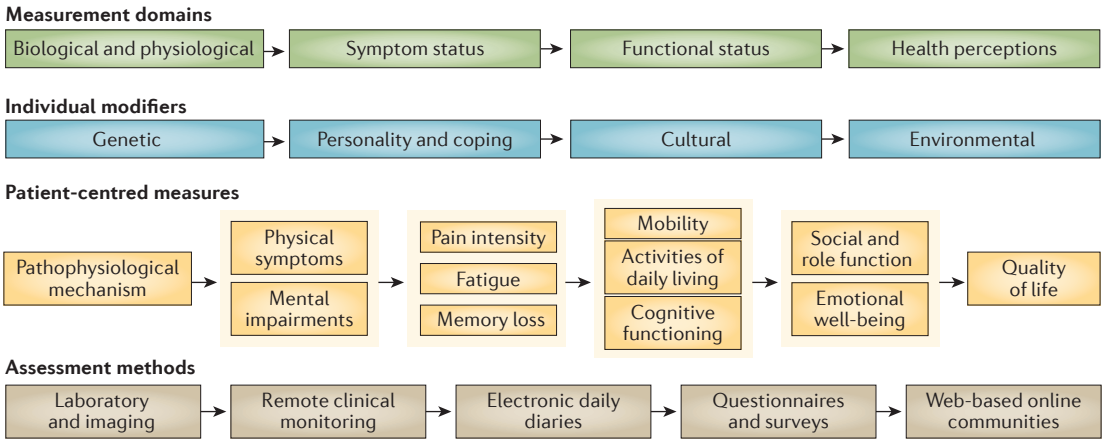

Figure 7 | **Illustration of the four major concepts in patient-reported outcomes.** The domains, individual modifiers and assessment methods for the multidimensional quality-of-life construct are shown in relation to selected patient-centred measures.

the basis of outcomes such as QOL, satisfaction and treatment adherence. Therefore, future diabetes research should be designed to gather high-quality scientific evidence of comparative treatment effectiveness on the basis of patient-centred outcomes.

QOL is multifaceted and can be assessed using several techniques (FIG. 7). Effective measurement of patient-centred outcomes poses challenges for clinical researchers, when deciding among the hundreds of available generic and disease-specific questionnaires (for example, see PROQOLID (http://www.qolid.org/proqolid)). Although QOL outcomes measured through structured, clinic-based, self-administered questionnaires have been found to be responsive to the effects of therapeutic interventions — such as symptoms of diabetes, changes in HbA1c, adverse effects, weight changes and glycaemic variability[264,265] — they are artificially restrictive and typically undertaken in the clinic at relatively infrequent intervals.

Using newer electronic and mobile computing technologies, monitoring QOL in real time is now feasible, and offers a more efficient and accurate way to collect data and broaden the scientific assessment of QOL data to real-time surveillance and remote monitoring. Smartphones and tablets are much more effective for reporting acute diabetes-related and treatment-related events such as hypoglycaemia, gastrointestinal symptoms, cognitive problems and sleep disturbances than older technologies[266]. Furthermore, they allow for 'dynamic' questionnaires, bridging the gap between more-sensitive but more-burdensome longer 'static' questionnaires and less-sensitive but less-burdensome shorter forms by using item response theory and computer adaptive testing[267]. Most recently, big data methods have been used in patient-centred outcomes research for analysing electronic health records, web-based, crowd-sourced social media databanks, and intensively longitudinal, electronic remote patient-monitoring databases transmitted through glucose, blood pressure, weight and activity devices. These methods provide promising research opportunities for capturing patient functioning and feelings in real time and in real-life environments.

Outlook

Long-term normalization of blood glucose levels in T2DM depends on delaying or reversing failure of β-cell function to ensure appropriate insulin secretion and on improving insulin resistance. New avenues for treatment are currently in development[268] and might, in combination with existing drugs, bring change and enhance our ability to control glycaemia. Our ability to prevent and reverse advanced microvascular and macrovascular complications is limited, and new strategies, some currently under investigation, will be required to close this gap (FIG. 8).

Insulin secretion

Progression from altered glucose metabolism to overt diabetes occurs as the reduction in β-cell mass and function is further aggravated. Thus, an attractive intervention is one that will halt the progressive decline in β-cell mass and function and prevent the need for exogenous insulin replacement that otherwise follows[1]. Agents that suppress inflammation, including IL-1β blockers and salsalate (a potent inhibitor of NF-κB), have shown some promise in improving glycaemic control and β-cell function[143,269,270]. MicroRNAs play a pivotal part in the physiological and pathological processes involved in glucose metabolism by post-transcriptional regulation of gene expression. Particular microRNAs can regulate β-cell function[271], exposing key regulatory signalling pathways involved in restoration of β-cell mass, and provide a promising strategy for improving insulin secretion and β-cell health in T2DM. Identification of novel insulin secretagogues that act directly on β-cells and enteroendocrine K cells and L cells in the intestine are under investigation, and members of the G protein-coupled class of receptors have shown promise[272]. GLP1 receptor agonists induce β-cell proliferation in rodents[273], but studies in humans have not demonstrated a similar effect[237]. A series of novel signalling pathways have been reported to be strongly associated with β-cell mass restoration. For example, the PI3K– PKCζ pathway has been shown to augment glucose-mediated β-cell proliferation, and activation of PKCζ may provide a novel approach to increase human β-cell proliferation[274].

Glucose-stimulated insulin secretion

Mitochondrial metabolism is essential for normal β-cell function[275]. APPL1 proteins are reported to influence mitochondrial function and β-cells by maintaining the expression of several key genes involved in mitochondrial biogenesis[276]. APPL1 also contributes to the regulation of both first and second phases of glucose-stimulated insulin secretion[276] and therefore has potential as a therapeutic target for anti-T2DM drug discovery. Other agents that improve mitochondrial function, including the regulators of NAD-dependent protein deacetylase sirtuin 1, peroxisome proliferator-activated protein kinase and uncoupling protein 2 (UCP2), may prove to be effective in the therapeutic intervention of T2DM[277–279].

Glucokinase is a key therapeutic target and serves as the 'glucose sensor' and glycolysis activator in β-cells. However, multiple glucokinase activators have failed because of lack of efficacy or adverse effects[280]. Glucagon receptor antagonists have shown good clinical efficacy, although α-cell hyperplasia and increased levels of hepatic aminotransferases may limit their usefulness[281]. Gluconeogenic inhibitors have shown some efficacy[282–284], but safety issues (hypoglycaemia and lactic acidosis) are a concern.

Islet transplantation faces many hurdles[285], but encapsulated islets hold promise[286]. The practicality of transforming stem cells into insulin-secreting β-cells that are responsive to glucose[287] is a long way off. The creation of stem cells that imitate natural healthy β-cells represents another option[287]. However, the concept that stressed β-cells in patients with diabetes dedifferentiate into other islet cells raises hopes for reversing this process[288].

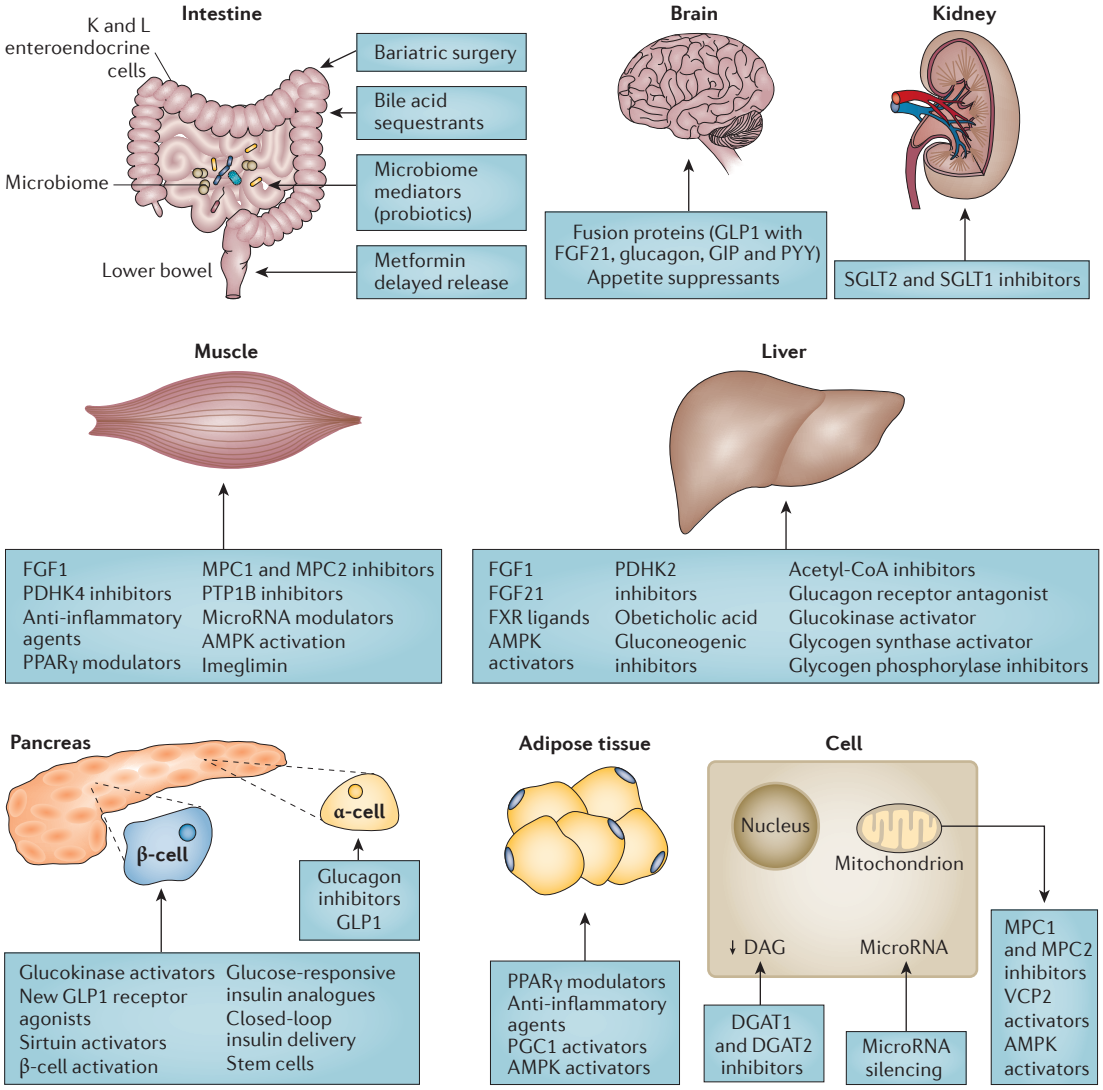

Figure 8 | **Potential therapeutic targets in T2DM management.** Schematic representation of the different targets in type 2 diabetes mellitus (T2DM) organized per tissue. AMPK, AMP-activated protein kinase; DAG, diacylglycerol; DGAT, DAG acyltransferase; FGF, fibroblast growth factor; FXR, farnesoid X nuclear receptor; GIP, gastric inhibitory polypeptide; GLP1, glucagon-like peptide 1; MPC, mitochondrial pyruvate carrier; PDHK, pyruvate dehydrogenase kinase; PGC1, PPARγ coactivator 1; PPARγ, peroxisome proliferator-activated receptor-γ; PTP1B, protein tyrosine phosphatase 1B; PYY, peptide YY; SGLT, sodium/glucose co-transporter; VCP2, viral citrullinated peptide 2.

In patients with T2DM who have minimal β-cell reserves, intensive continuous subcutaneous insulin infusion has proved to be very effective[289]. In contrast to the accuracy needed for insulin delivery in insulin-sensitive T1DM, the larger doses of insulin and underlying insulin resistance in T2DM enable the use of much simpler pump devices. Hopefully, this will result in the introduction of less-sophisticated and low-price pumps into the market. Conversely, closed-loop insulin delivery systems that consist of an insulin pump that delivers insulin based on an algorithm whose inputs are derived from a continuous glucose monitor are advancing quickly in clinical studies[289,290], and this might be an attractive option for insulin-dependent, poorly controlled T2DM. Insulin administration via injection is a limiting factor for its broader use. Inhaled insulin with improved pharmacokinetic and pharmacodynamic profiles makes this option more appealing to patients[291]. Another attractive option is oral insulin, which is currently in clinical trials and hopefully will mature into a simple and safe alternative for insulin delivery[292].

Insulin sensitivity

There is a major need for novel insulin-sensitizing agents, and many new agents show promise in humans. New metformin preparations target the lower bowel, effectively reducing HbA1c while minimizing metformin exposure[293]. In addition, selective PPARγ modulators have shown some efficacy as insulin sensitizers[294]. Compounds targeting mitochondrial proteins (mitochondrial pyruvate carrier 1 (MPC1) and MPC2) have shown efficacy[295]. Derivatives of fibroblast growth factor 1 improve hepatic and muscle insulin sensitivity in animals[296] and reduce plasma glucose levels in patients with T2DM[297]. Inhibitors of pyruvate dehydrogenase kinase 4 (PDHK4) increase pyruvate oxidation in muscle and reduce the supply of gluconeogenic precursors (lactate and alanine) to the liver, whereas inhibition of PDHK2 in the liver decreases gluconeogenesis[298]. Imeglimin, the first member of a new tetrahydrotriazine-containing class of oral antidiabetics (glimins), has modest HbA1c-lowering efficacy and augments both insulin sensitivity and insulin secretion[299,300]. UCP2 activators have similarly been shown to improve hepatic and muscle insulin sensitivity in rodents.

Accumulation of toxic lipid metabolites (DAG, fatty acid acyl-CoAs and ceramides) in muscle and the liver causes severe insulin resistance. Inhibitors of DAG acyltransferase 1 (DGAT1) and DGAT2 have yielded conflicting results[301,302]. Blockade of *de novo* lipogenesis with inhibitors of acetyl-CoA carboxylase reduces liver fat and increases hepatic insulin sensitivity in preclinical studies[303]. Liver-targeted mitochondrial uncouplers have been shown to reduce liver fat and content and improve insulin sensitivity in mice[304,305]. Weight loss drugs (topiramate and phentermine extended-release, lorcaserin, bupropion and naltrexone, and high-dose liraglutide) promote fat removal from muscle and the liver and improve insulin sensitivity and glycaemic control in T2DM[306]. Bariatric surgery provides long-term remission of T2DM[307]. The farnesoid X nuclear receptor ligand obeticholic acid[308] and bile acid sequestrants[309] might prove to be useful in treating T2DM. Novel fusion proteins, including GLP1 with fibroblast growth factor 21, glucagon, GIP or peptide YY, which promote weight loss and enhance insulin sensitivity in rodents, are in development[310]. Inhibitors of protein tyrosine phosphatase 1B, a cytosolic non-receptor PTPase that has been implicated as a negative regulator of insulin signal transduction, have received interest[311]. Several microRNAs are upregulated in diabetes and obesity, and their silencing improves insulin sensitivity[312].

Specific microbiome profiles render individuals prone to develop obesity and altered glucose metabolism[313]. The ability to identify protective microbiome profiles might provide a key to the development of obesity and diabetes interventions. It remains to be determined whether specific dietary components are involved in microbiome changes and induce unfavourable transitions. Probiotics or pharmacological manipulation of microbiome elements that favour more 'healthy' flora may prove to be useful in stemming the 'twin epidemics' of obesity and T2DM[313]. Surgical rearrangement of the gastrointestinal tract has shown remarkable efficacy in treating obese patients with T2DM[307,314]. Development of minimally invasive reversible procedures, such as the duodenal sleeve and temporary mucosal barriers, might replace surgery in the near future.

Comorbidities

There is great need to address short- and long-term diabetic complications. The most promising therapy for the near future is the use of drug combinations (dual or triple) that address the pathophysiological abnormalities responsible for β-cell dysfunction and insulin resistance and that normalize plasma glucose levels[198–200] (FIG. 3). The optimal candidates for this therapy are patients at the very early stage of their disease or at the prediabetes state[7].

Hypoglycaemia remains a critical barrier for intensification of care, especially in patients who require insulin, and poses serious immediate and long-term risks. Continuous glucose monitoring with pre-set alarms and use of therapeutic agents or regimens that minimize the risk of hypoglycaemia are available options. A self-regulating insulin that is responsive to blood sugar levels (SmartCells) is currently under development.

Treatment of established microvascular complications remains a major unmet need. Anti-VEGF (vascular endothelial growth factor) therapy has changed the outcome in many patients with advanced retinopathy, but more novel therapies are needed. C-peptide replacement therapy[315] and ocular inhibition of kallikreins and kinin receptor antagonists offer new therapeutic avenues[316]. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers slow progression of nephropathy but do not reverse it[317]. Endothelin inhibitors or agents that prevent AGE accumulation are in Phase III studies for prevention of microvascular complications[318,319]. SGLT2 inhibitors also are being investigated for the prevention of diabetic nephropathy[250]. Although we have agents that can ameliorate symptoms of diabetic neuropathy, there is a need for molecules that will prevent its development and progression.

Cardiovascular morbidity and mortality, the major cause of death in T2DM, is increased twofold–threefold in patients with T2DM[320]. Hyperglycaemia is a weak risk factor for cardiovascular disease, and the factors (other than hypertension, dyslipidaemia and enhanced coagulation) that are responsible for the increased cardiovascular risk in T2DM remain obscure. As T2DM is an inflammatory disease, an anti-inflammatory approach initiated early in combination with normalization of cardiovascular risk factors[17] before the clinical appearance of macrovascular disease may prove to be effective.

1. DeFronzo, R. A. Banting lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes* **58**, 773–795 (2009).
A classic review of the aetiology of T2DM, with a therapeutic approach based on its pathophysiology.
2. Abdul-Ghani, M. A., Tripathy, D. & DeFronzo, R. A. Contributions of β-cell dysfunction and insulin resistance to the pathogenesis of impaired glucose tolerance and impaired fasting glucose. *Diabetes Care* **29**, 1130–1139 (2006).
3. Gerstein, H. C. *et al.* Annual incidence and relative risk of diabetes in people with various categories of dysglycemia: a systematic overview and meta-analysis of prospective studies. *Diabetes Res. Clin. Pract.* **78**, 305–312 (2007).
4. Hawa, M. I. *et al.* Adult-onset autoimmune diabetes in Europe is prevalent with a broad clinical phenotype: action LADA 7. *Diabetes Care* **36**, 908–913 (2013).
5. Gardner, D. S. & Tai, E. S. Clinical features and treatment of maturity onset diabetes of the young (MODY). *Diabetes. Metab. Syndr. Obes.* **5**, 101–108 (2012).
6. American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care* **37**, S14–S80 (2014).
A comprehensive overview of the standards of medical care published by the ADA.
7. DeFronzo, R. A. & Abdul-Ghani, M. A. Preservation of β-cell function: the key to diabetes prevention. *J. Clin. Endocrinol. Metab.* **96**, 2354–2366 (2011).
8. Ferrannini, E., Gastaldelli, A. & Iozzo, P. Pathophysiology of prediabetes. *Med. Clin. North Am.* **95**, 327–339 (2011).
9. Garvey, W. T. *et al.* Prevention of type 2 diabetes in subjects with prediabetes and metabolic syndrome treated with phentermine and topiramate extended release. *Diabetes Care* **37**, 912–921 (2014).
10. Nathan, D. M. *et al.* Impaired fasting glucose and impaired glucose tolerance: implications for care. *Diabetes Care* **30**, 753–759 (2007).
11. DeFronzo, R. A. *et al.* Pioglitazone for diabetes prevention in impaired glucose tolerance. *N. Engl. J. Med.* **364**, 1104–1115 (2011).
A large prospective study demonstrating the efficacy of thiazolidinediones in preventing the progression of IGT to T2DM.
12. Zinman, B. *et al.* Low-dose combination therapy with rosiglitazone and metformin to prevent type 2 diabetes mellitus (CANOE trial): a double-blind randomised controlled study. *Lancet* **376**, 103–111 (2010).
13. Dansinger, M. L., Tatsioni, A., Wong, J. B., Chung, M. & Balk, E. M. Meta-analysis: the effect of dietary counseling for weight loss. *Ann. Intern. Med.* **147**, 41–50 (2007).
14. Purcell, K. *et al.* The effect of rate of weight loss on long-term weight management: a randomised controlled trial. *Lancet Diabetes Endocrinol.* **2**, 954–962 (2014).
15. Ali, M. K., Echouffo-Tcheugui, J. & Williamson, D. F. How effective were lifestyle interventions in real-world settings that were modeled on the Diabetes Prevention Program? *Health Aff. (Millwood)* **31**, 67–75 (2012).
16. Tuomilehto, J. *et al.* Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N. Engl. J. Med.* **344**, 1343–1350 (2001).
17. Inzucchi, S. E. *et al.* Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* **35**, 1364–1379 (2012).
ADA position statement on the treatment of T2DM, advocating a stepped care approach starting with metformin.
18. American Association of Clinical Endocrinologists. AACE Comprehensive Diabetes Algorithm 2013 Consensus Statement. *Endocr. Pract. Suppl.* **1**, 1–87 (2015).
AACE position statement on the treatment of T2DM, advocating initial monotherapy or combination therapy based upon the starting HbA1c, and recommending various antidiabetic medications as initial therapy.
19. Pozzilli, P. *et al.* The A1C and ABCD of glycaemia management in type 2 diabetes: a physician's personalized approach. *Diabetes Metab. Res. Rev.* **26**, 239–244 (2010).
The first published report by key opinion leaders recommending individualized therapy based on the age and body weight of patients, the presence or absence of complications, and duration and aetiology of disease.
20. International Diabetes Federation. IDF Diabetes Atlas 6th Edition. *IDF* [online], http://www.idf.org/sites/default/files/EN_6E_Atlas_Full_0.pdf (2013).
21. Hu, F. B. Globalization of diabetes: the role of diet, lifestyle, and genes. *Diabetes Care* **34**, 1249–1257 (2011).
An important study emphasizing the role of diet, physical activity and genes — beyond obesity — in the diabetes epidemic that is engulfing Asian countries as they are exposed to westernization.
22. Chan, J. C. *et al.* Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *JAMA* **301**, 2129–2140 (2009).
23. Ley, S. H., Hamdy, O., Mohan, V. & Hu, F. B. Prevention and management of type 2 diabetes: dietary components and nutritional strategies. *Lancet* **383**, 1999–2007 (2014).
24. Grøntved, A., Rimm, E. B., Willett, W. C., Andersen, L. B. & Hu, F. B. A prospective study of weight training and risk of type 2 diabetes mellitus in men. *Arch. Intern. Med.* **172**, 1306–1312 (2012).
25. Grøntved, A. & Hu, F. B. Television viewing and risk of type 2 diabetes, cardiovascular disease, and all-cause mortality: a meta-analysis. *JAMA* **305**, 2448–2455 (2011).
26. Cappuccio, F. P., D'Elia, L., Strazzullo, P. & Miller, M. A. Quantity and quality of sleep and incidence of type 2 diabetes: a systematic review and meta-analysis. *Diabetes Care* **33**, 414–420 (2009).
27. Pan, A., Schernhammer, E. S., Sun, Q. & Hu, F. B. Rotating night shift work and risk of type 2 diabetes: two prospective cohort studies in women. *PLoS Med.* **8**, e1001141 (2011).
28. Barnett, A. H., Eff, C., Leslie, R. D. & Pyke, D. A. Diabetes in identical twins. A study of 200 pairs. *Diabetologia* **20**, 87–93 (1981).
29. Wang, Y. C., McPherson, K., Marsh, T., Gortmaker, S. L. & Brown, M. Health and economic burden of the projected obesity trends in the USA and the UK. *Lancet* **378**, 815–825 (2011).
30. Wang, X. *et al.* Inflammatory markers and risk of type 2 diabetes: a systematic review and meta-analysis. *Diabetes Care* **36**, 166–175 (2013).
31. Li, S., Shin, H. J., Ding, E. L. & van Dam, R. M. Adiponectin levels and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA* **302**, 179–188 (2009).
32. Ding, E. L. *et al.* Sex hormone-binding globulin and risk of type 2 diabetes in women and men. *N. Engl. J. Med.* **361**, 1152–1163 (2009).
33. Wang, T. J. *et al.* Metabolite profiles and the risk of developing diabetes. *Nat. Med.* **17**, 448–453 (2011).
34. Esteve, E., Ricart, W. & Fernández-Real, J.-M. Gut microbiota interactions with obesity, insulin resistance and type 2 diabetes: did gut microbiote co-evolve with insulin resistance? *Curr. Opin. Clin. Nutr. Metab. Care* **14**, 483–490 (2011).
35. Hu, F. B. *et al.* Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *N. Engl. J. Med.* **345**, 790–797 (2001).
36. Schellenberg, E. S., Dryden, D. M., Vandermeer, B., Ha, C. & Korownyk, C. Lifestyle interventions for patients with and at risk for type 2 diabetes. *Ann. Intern. Med.* **159**, 543–551 (2013).
A comprehensive review of the effectiveness of lifestyle intervention in the treatment of T2DM, emphasizing that, although initially successful, most subjects with diabetes regain the majority of lost weight over the subsequent 3–5 years.
37. DeFronzo, R. A. Insulin resistance, lipotoxicity, type 2 diabetes and atherosclerosis: the missing links. The Claude Bernard Lecture 2009. *Diabetologia* **53**, 1270–1287 (2010).
A comprehensive review describing the role of excess tissue lipid deposition in the development of insulin resistance, β-cell failure and atherosclerotic cardiovascular disease: that is, lipotoxicity.
38. Hemminki, K., Li, X., Sundquist, K. & Sundquist, J. Familial risks for type 2 diabetes in Sweden. *Diabetes Care* **33**, 293–297 (2010).
39. Groop, L. *et al.* Metabolic consequences of a family history of NIDDM (the Botnia study): evidence for sex-specific parental effects. *Diabetes* **45**, 1585–1593 (1996).
40. Lyssenko, V. *et al.* Predictors of and longitudinal changes in insulin sensitivity and secretion preceding onset of type 2 diabetes. *Diabetes* **54**, 166–174 (2005).
41. Grant, S. F. *et al.* Variant of transcription factor 7-like 2 (*TCF7L2*) gene confers risk of type 2 diabetes. *Nat. Genet.* **38**, 320–323 (2006).
42. Lyssenko, V. *et al.* Mechanisms by which common variants in the *TCF7L2* gene increase risk of type 2 diabetes. *J. Clin. Invest.* **117**, 2155–2163 (2007).
43. Sladek, R. *et al.* A genome-wide association study identifies novel risk loci for type 2 diabetes. *Nature* **445**, 881–885 (2007).
44. Saxena, R. *et al.* Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. *Science* **316**, 1331–1336 (2007).
45. Morris, A. P. *et al.* Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. *Nat. Genet.* **44**, 981–990 (2012).
46. Flannick, J. *et al.* Loss-of-function mutations in *SLC30A8* protect against type 2 diabetes. *Nat. Genet.* **46**, 357–363 (2014).
47. Lyssenko, V. *et al.* Common variant in *MTNR1B* associated with increased risk of type 2 diabetes and impaired early insulin secretion. *Nat. Genet.* **41**, 82–88 (2009).
48. Rosengren, A. H. *et al.* Overexpression of alpha2A-adrenergic receptors contributes to type 2 diabetes. *Science* **327**, 217–220 (2010).
49. Tang, Y. *et al.* Genotype-based treatment of type 2 diabetes with an α2A-adrenergic receptor antagonist. *Sci. Transl Med.* **6**, 257ra139 (2014).
These paper provides an example in which a genetic finding in an animal model of diabetes has been translated into a drug target in humans, the *ADRA2A* gene.
50. De Jesus, D. F. & Kulkarni, R. N. Epigenetic modifiers of islet function and mass. *Trends Endocrinol. Metab.* **25**, 628–636 (2014).
51. Ozcan, S. Minireview: microRNA function in pancreatic β cells. *Mol. Endocrinol.* **28**, 1922–1933 (2014).
52. Lyssenko, V. *et al.* Clinical risk factors, DNA variants, and the development of type 2 diabetes. *N. Engl. J. Med.* **359**, 2220–2232 (2008).
This paper presents a genetic explanation for the development of T2DM.
53. Travers, M. E. *et al.* Insights into the molecular mechanism for type 2 diabetes susceptibility at the *KCNQ1* locus from temporal changes in imprinting status in human islets. *Diabetes* **62**, 987–992 (2013).
54. Gulli, G., Ferrannini, E., Stern, M., Haffner, S. & DeFronzo, R. A. The metabolic profile of NIDDM is fully established in glucose-tolerant offspring of two Mexican-American NIDDM parents. *Diabetes* **41**, 1575–1586 (1992).

55. Martin, B. C. *et al.* Role of glucose and insulin resistance in development of type 2 diabetes mellitus: results of a 25-year follow-up study. *Lancet* **340**, 925–929 (1992).
56. Ferrannini, E. & Mari, A. β-cell function in type 2 diabetes. *Metabolism* **63**, 1217–1227 (2014).
57. Kahn, S. E., Cooper, M. E. & Del Prato, S. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. *Lancet* **383**, 1068–1083 (2014).
58. Muller, D. C., Elahi, D., Tobin, J. D. & Andres, R. Insulin response during the oral glucose tolerance test: the role of age, sex, body fat and the pattern of fat distribution. *Aging (Milano)* **8**, 13–21 (1996).
59. Nauck, M. A., Vardarli, I., Deacon, C. F., Holst, J. J. & Meier, J. J. Secretion of glucagon-like peptide-1 (GLP-1) in type 2 diabetes: what is up, what is down? *Diabetologia* **54**, 10–18 (2011).
60. Madsbad, S. The role of glucagon-like peptide-1 impairment in obesity and potential therapeutic implications. *Diabetes Obes. Metab.* **16**, 9–21 (2014).
61. Bays, H., Mandarino, L. & DeFronzo, R. A. Role of the adipocyte, free fatty acids, and ectopic fat in pathogenesis of type 2 diabetes mellitus: peroxisomal proliferator-activated receptor agonists provide a rational therapeutic approach. *J. Clin. Endocrinol. Metab.* **89**, 463–478 (2004).
62. Perry, R. J., Samuel, V. T., Petersen, K. F. & Shulman, G. I. The role of hepatic lipids in hepatic insulin resistance and type 2 diabetes. *Nature* **510**, 84–91 (2014).
An excellent review of the specific lipid varieties and the molecular events through which they cause insulin resistance in the liver.
63. Bensellam, M., Laybutt, D. R. & Jonas, J.-C. The molecular mechanisms of pancreatic β-cell glucotoxicity: recent findings and future research directions. *Mol. Cell. Endocrinol.* **364**, 1–27 (2012).
64. Ritzel, R. A., Meier, J. J., Lin, C.-Y., Veldhuis, J. D. & Butler, P. C. Human islet amyloid polypeptide oligomers disrupt cell coupling, induce apoptosis, and impair insulin secretion in isolated human islets. *Diabetes* **56**, 65–71 (2007).
65. Collins, S., Pi, J. & Yehuda-Shnaidman, E. Uncoupling and reactive oxygen species (ROS) — a double-edged sword for β-cell function? "Moderation in all things". *Best Pract. Res. Clin. Endocrinol. Metab.* **26**, 753–758 (2012).
66. Cabrera, O. *et al.* The unique cytoarchitecture of human pancreatic islets has implications for islet cell function. *Proc. Natl Acad. Sci. USA* **103**, 2334–2339 (2006).
67. Hodson, D. J. *et al.* Lipotoxicity disrupts incretin-regulated human β cell connectivity. *J. Clin. Invest.* **123**, 4182–4194 (2013).
68. Brandhorst, H., Brandhorst, D., Brendel, M. D., Hering, B. J. & Bretzel, R. G. Assessment of intracellular insulin content during all steps of human islet isolation procedure. *Cell Transplant.* **7**, 489–495 (1998).
69. Rahier, J., Guiot, Y., Goebbels, R. M., Sempoux, C. & Henquin, J. C. Pancreatic β-cell mass in European subjects with type 2 diabetes. *Diabetes Obes. Metab.* **10** (Suppl. 4), 32–42 (2008).
A post-mortem study demonstrating a decline in β-cell mass with preservation of α-cell mass in individuals with T2DM.
70. Marselli, L. *et al.* Are we overestimating the loss of beta cells in type 2 diabetes? *Diabetologia* **57**, 362–365 (2014).
71. Marchetti, P. *et al.* The endoplasmic reticulum in pancreatic beta cells of type 2 diabetes patients. *Diabetologia* **50**, 2486–2494 (2007).
72. Marchetti, P. & Masini, M. Autophagy and the pancreatic beta-cell in human type 2 diabetes. *Autophagy* **5**, 1055–1056 (2009).
73. Gupta, D. & Leahy, J. L. Islet amyloid and type 2 diabetes: overproduction or inadequate clearance and detoxification? *J. Clin. Invest.* **124**, 3292–3294 (2014).
74. Mezza, T. *et al.* Insulin resistance alters islet morphology in nondiabetic humans. *Diabetes* **63**, 994–1007 (2014).
This work in human islets describes the impact of insulin resistance on the relative proportion of α-cells and β-cells, and the functional consequences — in terms of insulin and glucagon secretion — of this chronic adaptation.
75. Deng, S. *et al.* Structural and functional abnormalities in the islets isolated from type 2 diabetic subjects. *Diabetes* **53**, 624–632 (2004).
76. Igoillo-Esteve, M. *et al.* Palmitate induces a pro-inflammatory response in human pancreatic islets that mimics *CCL2* expression by beta cells in type 2 diabetes. *Diabetologia* **53**, 1395–1405 (2010).
77. Giacca, A., Xiao, C., Oprescu, A. I., Carpentier, A. C. & Lewis, G. F. Lipid-induced pancreatic β-cell dysfunction: focus on *in vivo* studies. *Am. J. Physiol. Endocrinol. Metab.* **300**, E255–E262 (2010).
78. Halban, P. A. *et al.* β-cell failure in type 2 diabetes: postulated mechanisms and prospects for prevention and treatment. *J. Clin. Endocrinol. Metab.* **99**, 1983–1992 (2014).
79. Ferrannini, E. *et al.* Natural history and physiological determinants of changes in glucose tolerance in a non-diabetic population: the RISC Study. *Diabetologia* **54**, 1507–1516 (2011).
This longitudinal study of non-diabetic subjects identifies baseline insulin resistance and β-cell dysfunction as predictors of future dysglycaemia.
80. Michaliszyn, S. F. *et al.* β-cell function, incretin effect, and incretin hormones in obese youth along the span of glucose tolerance from normal to prediabetes to type 2 diabetes. *Diabetes* **63**, 3846–3855 (2014).
81. Mari, A. *et al.* Mechanisms of the incretin effect in subjects with normal glucose tolerance and patients with type 2 diabetes. *PLoS ONE* **8**, e73154 (2013).
82. Holst, J. J., Knop, F. K., Vilsbøll, T., Krarup, T. & Madsbad, S. Loss of incretin effect is a specific, important, and early characteristic of type 2 diabetes. *Diabetes Care* **34**, S251–S257 (2011).
83. Camastra, S. *et al.* Long-term effects of bariatric surgery on meal disposal and β-cell function in diabetic and nondiabetic patients. *Diabetes* **62**, 3709–3717 (2013).
84. Ferrannini, E. The stunned β cell: a brief history. *Cell Metab.* **11**, 349–352 (2010).
85. Shulman, G. I. *et al.* Quantitation of muscle glycogen synthesis in normal subjects and subjects with non-insulin-dependent diabetes by 13C nuclear magnetic resonance spectroscopy. *N. Engl. J. Med.* **322**, 223–228 (1990).
This study demonstrated that defects in insulin-stimulated muscle glycogen synthesis was the major factor responsible for whole-body insulin resistance in patients with T2DM.
86. Groop, L. C. *et al.* Glucose and free fatty acid metabolism in non-insulin-dependent diabetes mellitus. Evidence for multiple sites of insulin resistance. *J. Clin. Invest.* **84**, 205–213 (1989).
87. Guilherme, A., Virbasius, J. V., Puri, V. & Czech, M. P. Adipocyte dysfunctions linking obesity to insulin resistance and type 2 diabetes. *Nat. Rev. Mol. Cell Biol.* **9**, 367–377 (2008).
88. Gerich, J. E., Meyer, C., Woerle, H. J. & Stumvoll, M. Renal gluconeogenesis: its importance in human glucose homeostasis. *Diabetes Care* **24**, 382–391 (2001).
89. Honka, H. *et al.* Validation of [^{18}F]fluorodeoxyglucose and positron emission tomography (PET) for the measurement of intestinal metabolism in pigs, and evidence of intestinal insulin resistance in patients with morbid obesity. *Diabetologia* **56**, 893–900 (2013).
90. Meijer, R. I. *et al.* Insulin-induced microvascular recruitment in skin and muscle are related and both are associated with whole-body glucose uptake. *Microcirculation* **19**, 494–500 (2012).
91. Blázquez, E., Velázquez, E., Hurtado-Carneiro, V. & Ruiz-Albusac, J. M. Insulin in the brain: its pathophysiological implications for states related with central insulin resistance, type 2 diabetes and Alzheimer's disease. *Front. Endocrinol. (Lausanne)* **5**, 161 (2014).
92. Kleinridders, A., Ferris, H. A., Cai, W. & Kahn, C. R. Insulin action in brain regulates systemic metabolism and brain function. *Diabetes* **63**, 2232–2243 (2014).
93. Kulkarni, R. N. *et al.* Tissue-specific knockout of the insulin receptor in pancreatic β cells creates an insulin secretory defect similar to that in type 2 diabetes. *Cell* **96**, 329–339 (1999).
An insightful study documenting that β-cell-specific insulin receptor knockout results in markedly impaired insulin secretion and overt diabetes, thereby providing a unifying mechanism whereby insulin resistance explains both the defects in insulin-stimulated tissue glucose uptake and decreased insulin secretion.
94. Oliveira, J. M., Rebuffat, S. A., Gasa, R. & Gomis, R. Targeting type 2 diabetes: lessons from a knockout model of insulin receptor substrate 2. *Can. J. Physiol. Pharmacol.* **92**, 613–620 (2014).
95. Samuel, V. T. & Shulman, G. I. Mechanisms for insulin resistance: common threads and missing links. *Cell* **148**, 852–871 (2012).
An excellent review of the molecular mechanism responsible for insulin resistance in T2DM and obesity.
96. Magnusson, I., Rothman, D. L., Katz, L. D., Shulman, R. G. & Shulman, G. I. Increased rate of gluconeogenesis in type II diabetes mellitus. A 13C nuclear magnetic resonance study. *J. Clin. Invest.* **90**, 1323–1327 (1992).
This study demonstrated that increased rates of hepatic glucose production in patients with poorly controlled T2DM could entirely be attributed to increased rates of gluconeogenesis.
97. Matsuda, M. *et al.* Glucagon dose-response curve for hepatic glucose production and glucose disposal in type 2 diabetic patients and normal individuals. *Metabolism* **51**, 1111–1119 (2002).
98. Samuel, V. T. *et al.* Fasting hyperglycemia is not associated with increased expression of PEPCK or G6Pc in patients with type 2 diabetes. *Proc. Natl Acad. Sci. USA* **106**, 12121–12126 (2009).
99. Baron, A. D., Schaeffer, L., Shragg, P. & Kolterman, O. G. Role of hyperglucagonemia in maintenance of increased rates of hepatic glucose output in type II diabetics. *Diabetes* **36**, 274–283 (1987).
100. DeFronzo, R. A., Ferrannini, E., Hendler, R., Wahren, J. & Felig, P. Influence of hyperinsulinemia, hyperglycemia, and the route of glucose administration on splanchnic glucose exchange. *Proc. Natl Acad. Sci. USA* **75**, 5173–5177 (1978).
101. Ferrannini, E. *et al.* The disposal of an oral glucose load in patients with non-insulin-dependent diabetes. *Metabolism* **37**, 79–85 (1988).
102. DeFronzo, R. A. *et al.* Characterization of renal glucose reabsorption in response to dapagliflozin in healthy subjects and subjects with type 2 diabetes. *Diabetes Care* **36**, 3169–3176 (2013).
103. Barrett, E. J., Wang, H., Upchurch, C. T. & Liu, Z. Insulin regulates its own delivery to skeletal muscle by feed-forward actions on the vasculature. *Am. J. Physiol. Endocrinol. Metab.* **301**, E252–E263 (2011).
104. Baron, A. D. Hemodynamic actions of insulin. *Am. J. Physiol.* **267**, E187–E202 (1994).
105. Krüger, M. *et al.* Dissection of the insulin signaling pathway via quantitative phosphoproteomics. *Proc. Natl Acad. Sci. USA* **105**, 2451–2456 (2008).
106. Cusi, K. *et al.* Insulin resistance differentially affects the PI 3-kinase- and MAP kinase-mediated signaling in human muscle. *J. Clin. Invest.* **105**, 311–320 (2000).
The first study in humans with T2DM to demonstrate impaired insulin signal transduction through the IRS1–PI3K pathway in muscle, with normal to increased insulin signalling through the MAPK pathway.
107. Krook, A. *et al.* Characterization of signal transduction and glucose transport in skeletal muscle from type 2 diabetic patients. *Diabetes* **49**, 284–292 (2000).
108. Copps, K. D. & White, M. F. Regulation of insulin sensitivity by serine/threonine phosphorylation of insulin receptor substrate proteins IRS1 and IRS2. *Diabetologia* **55**, 2565–2582 (2012).
109. Bouzakri, K. *et al.* IRS-1 serine phosphorylation and insulin resistance in skeletal muscle from pancreas transplant recipients. *Diabetes* **55**, 785–791 (2006).
110. Hiratani, K. *et al.* Roles of mTOR and JNK in serine phosphorylation, translocation, and degradation of IRS-1. *Biochem. Biophys. Res. Commun.* **335**, 836–842 (2005).
111. Krssak, M. *et al.* Intramyocellular lipid concentrations are correlated with insulin sensitivity in humans: a 1H NMR spectroscopy study. *Diabetologia* **42**, 113–116 (1999).
112. Petersen, K. F. *et al.* Leptin reverses insulin resistance and hepatic steatosis in patients with severe lipodystrophy. *J. Clin. Invest.* **109**, 1345–1350 (2002).
113. Petersen, K. F. *et al.* Reversal of nonalcoholic hepatic steatosis, hepatic insulin resistance, and hyperglycemia by moderate weight reduction in patients with type 2 diabetes. *Diabetes* **54**, 603–608 (2005).
114. Lara-Castro, C. & Garvey, W. T. Intracellular lipid accumulation in liver and muscle and the insulin resistance syndrome. *Endocrinol. Metab. Clin. North Am.* **37**, 841–856 (2008).
115. Yu, C. *et al.* Mechanism by which fatty acids inhibit insulin activation of insulin receptor substrate-1 (IRS-1)-associated phosphatidylinositol 3-kinase activity in muscle. *J. Biol. Chem.* **277**, 50230–50236 (2002).

116. Bezy, O. *et al.* PKCδ regulates hepatic insulin sensitivity and hepatosteatosis in mice and humans. *J. Clin. Invest.* **121**, 2504–2517 (2011).
117. Samuel, V. T. *et al.* Mechanism of hepatic insulin resistance in non-alcoholic fatty liver disease. *J. Biol. Chem.* **279**, 32345–32353 (2004).
118. Samuel, V. T. *et al.* Inhibition of protein kinase Cε prevents hepatic insulin resistance in nonalcoholic fatty liver disease. *J. Clin. Invest.* **117**, 739–745 (2007).
119. Choi, C. S. *et al.* Suppression of diacylglycerol acyltransferase-2 (*DGAT2*), but not *DGAT1*, with antisense oligonucleotides reverses diet-induced hepatic steatosis and insulin resistance. *J. Biol. Chem.* **282**, 22678–22688 (2007).
120. Morino, K. *et al.* Reduced mitochondrial density and increased IRS-1 serine phosphorylation in muscle of insulin-resistant offspring of type 2 diabetic parents. *J. Clin. Invest.* **115**, 3587–3593 (2005).
121. Szendroedi, J. *et al.* Role of diacylglycerol activation of PKCθ in lipid-induced muscle insulin resistance in humans. *Proc. Natl Acad. Sci. USA* **111**, 9597–9602 (2014).
122. Larsen, P. J. & Tennagels, N. On ceramides, other sphingolipids and impaired glucose homeostasis. *Mol. Metab.* **3**, 252–260 (2014).
123. Turpin, S. M. *et al.* Obesity-induced CerS6-dependent C16:0 ceramide production promotes weight gain and glucose intolerance. *Cell Metab.* **20**, 678–686 (2014).
124. Cantley, J. L. *et al.* CGI-58 knockdown sequesters diacylglycerols in lipid droplets/ER-preventing diacylglycerol-mediated hepatic insulin resistance. *Proc. Natl Acad. Sci. USA* **110**, 1869–1874 (2013).
125. Patti, M.-E. & Corvera, S. The role of mitochondria in the pathogenesis of type 2 diabetes. *Endocr. Rev.* **31**, 364–395 (2010).
Mitochondrial dysfunction as a causative factor in the development of insulin resistance in T2DM is reviewed.
126. Ritov, V. B. *et al.* Deficiency of subsarcolemmal mitochondria in obesity and type 2 diabetes. *Diabetes* **54**, 8–14 (2005).
127. Petersen, K. F. *et al.* Mitochondrial dysfunction in the elderly: possible role in insulin resistance. *Science* **300**, 1140–1142 (2003).
128. Petersen, K. F., Dufour, S., Befroy, D., Garcia, R. & Shulman, G. I. Impaired mitochondrial activity in the insulin-resistant offspring of patients with type 2 diabetes. *N. Engl. J. Med.* **350**, 664–671 (2004).
129. Mogensen, M. *et al.* Mitochondrial respiration is decreased in skeletal muscle of patients with type 2 diabetes. *Diabetes* **56**, 1592–1599 (2007).
130. Petersen, K. F., Dufour, S. & Shulman, G. I. Decreased insulin-stimulated ATP synthesis and phosphate transport in muscle of insulin-resistant offspring of type 2 diabetic parents. *PLoS Med.* **2**, e233 (2005).
131. Wang, C.-H., Wang, C.-C., Huang, H.-C. & Wei, Y.-H. Mitochondrial dysfunction leads to impairment of insulin sensitivity and adiponectin secretion in adipocytes. *FEBS J.* **280**, 1039–1050 (2013).
132. Rains, J. L. & Jain, S. K. Oxidative stress, insulin signaling, and diabetes. *Free Radic. Biol. Med.* **50**, 567–575 (2011).
133. Morino, K. *et al.* Regulation of mitochondrial biogenesis by lipoprotein lipase in muscle of insulin-resistant offspring of parents with type 2 diabetes. *Diabetes* **61**, 877–887 (2012).
134. Romeo, G. R., Lee, J. & Shoelson, S. E. Metabolic syndrome, insulin resistance, and roles of inflammation — mechanisms and therapeutic targets. *Arterioscler. Thromb. Vasc. Biol.* **32**, 1771–1776 (2012).
135. Arkan, M. C. *et al.* IKK-β links inflammation to obesity-induced insulin resistance. *Nat. Med.* **11**, 191–198 (2005).
136. De Alvaro, C., Teruel, T., Hernandez, R. & Lorenzo, M. Tumor necrosis factor α produces insulin resistance in skeletal muscle by activation of inhibitor κB kinase in a p38 MAPK-dependent manner. *J. Biol. Chem.* **279**, 17070–17078 (2004).
137. Howard, J. K. & Flier, J. S. Attenuation of leptin and insulin signaling by SOCS proteins. *Trends Endocrinol. Metab.* **17**, 365–371 (2006).
138. Lebrun, P. & Van Obberghen, E. SOCS proteins causing trouble in insulin action. *Acta Physiol. (Oxf.)* **192**, 29–36 (2008).
139. Uysal, K. T., Wiesbrock, S. M. & Hotamisligil, G. S. Functional analysis of tumor necrosis factor (TNF) receptors in TNF-α-mediated insulin resistance in genetic obesity. *Endocrinology* **139**, 4832–4838 (1998).
140. Ofei, F., Hurel, S., Newkirk, J., Sopwith, M. & Taylor, R. Effects of an engineered human anti-TNF-α antibody (CDP571) on insulin sensitivity and glycemic control in patients with NIDDM. *Diabetes* **45**, 881–885 (1996).
141. Kim, J. K. *et al.* Prevention of fat-induced insulin resistance by salicylate. *J. Clin. Invest.* **108**, 437–446 (2001).
142. Yuan, M. *et al.* Reversal of obesity- and diet-induced insulin resistance with salicylates or targeted disruption of *IKK*β. *Science* **293**, 1673–1677 (2001).
143. Goldfine, A. B. *et al.* The effects of salsalate on glycemic control in patients with type 2 diabetes: a randomized trial. *Ann. Intern. Med.* **152**, 346–357 (2010).
144. Lumeng, C. N. & Saltiel, A. R. Inflammatory links between obesity and metabolic disease. *J. Clin. Invest.* **121**, 2111–2117 (2011).
145. Nishimura, S. *et al.* $CD8^+$ effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity. *Nat. Med.* **15**, 914–920 (2009).
146. Feuerer, M. *et al.* Lean, but not obese, fat is enriched for a unique population of regulatory T cells that affect metabolic parameters. *Nat. Med.* **15**, 930–939 (2009).
147. Bertola, A. *et al.* Identification of adipose tissue dendritic cells correlated with obesity-associated insulin-resistance and inducing Th17 responses in mice and patients. *Diabetes* **61**, 2238–2247 (2012).
148. Cai, D. *et al.* Local and systemic insulin resistance resulting from hepatic activation of IKK-β and NF-κB. *Nat. Med.* **11**, 183–190 (2005).
149. Perry, R. J. *et al.* Hepatic acetyl CoA links adipose tissue inflammation to hepatic insulin resistance and type 2 diabetes. *Cell* **160**, 745–758 (2015).
150. Mori, M. A. *et al.* A systems biology approach identifies inflammatory abnormalities between mouse strains prior to development of metabolic disease. *Diabetes* **59**, 2960–2971 (2010).
151. Mauer, J. *et al.* Myeloid cell-restricted insulin receptor deficiency protects against obesity-induced inflammation and systemic insulin resistance. *PLoS Genet.* **6**, e1000938 (2010).
152. Shi, H. *et al.* TLR4 links innate immunity and fatty acid-induced insulin resistance. *J. Clin. Invest.* **116**, 3015–3025 (2006).
153. Ron, D. & Walter, P. Signal integration in the endoplasmic reticulum unfolded protein response. *Nat. Rev. Mol. Cell Biol.* **8**, 519–529 (2007).
154. Boden, G. *et al.* Increase in endoplasmic reticulum stress-related proteins and genes in adipose tissue of obese, insulin-resistant individuals. *Diabetes* **57**, 2438–2444 (2008).
155. Eizirik, D. L., Cardozo, A. K. & Cnop, M. The role for endoplasmic reticulum stress in diabetes mellitus. *Endocr. Rev.* **29**, 42–61 (2008).
A comprehensive review of ER stress and the UPR in the development of insulin resistance and obesity.
156. Gregor, M. F. *et al.* Endoplasmic reticulum stress is reduced in tissues of obese subjects after weight loss. *Diabetes* **58**, 693–700 (2009).
157. Ozawa, K. *et al.* The endoplasmic reticulum chaperone improves insulin resistance in type 2 diabetes. *Diabetes* **54**, 657–663 (2005).
158. Herschkovitz, A. *et al.* Common inhibitory serine sites phosphorylated by IRS-1 kinases, triggered by insulin and inducers of insulin resistance. *J. Biol. Chem.* **282**, 18018–18027 (2007).
159. Boden, G. Endoplasmic reticulum stress: another link between obesity and insulin resistance/inflammation? *Diabetes* **58**, 518–519 (2009).
160. Sengupta, S., Peterson, T. R. & Sabatini, D. M. Regulation of the mTOR complex 1 pathway by nutrients, growth factors, and stress. *Mol. Cell* **40**, 310–322 (2010).
161. Shah, O. J., Wang, Z. & Hunter, T. Inappropriate activation of the TSC/Rheb/mTOR/S6K cassette induces IRS1/2 depletion, insulin resistance, and cell survival deficiencies. *Curr. Biol.* **14**, 1650–1656 (2004).
162. Ozcan, U. *et al.* Loss of the tuberous sclerosis complex tumor suppressors triggers the unfolded protein response to regulate insulin signaling and apoptosis. *Mol. Cell* **29**, 541–551 (2008).
163. Park, S. W. *et al.* The regulatory subunits of PI3K, p85α and p85β, interact with XBP-1 and increase its nuclear translocation. *Nat. Med.* **16**, 429–437 (2010).
164. Stratton, I. M. *et al.* Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* **321**, 405–412 (2000).
A seminal UK Prospective Diabetes Study study unequivocally demonstrating that improved glycaemic control reduced the incidence of microvascular, and to a lesser extent, macrovascular complications in patients with T2DM.
165. Holman, R. R., Paul, S. K., Bethel, M. A., Matthews, D. R. & Neil, H. A. 10-year follow-up of intensive glucose control in type 2 diabetes. *N. Engl. J. Med.* **359**, 1577–1589 (2008).
A long-term follow-up of the UK Prospective Diabetes Study showing that early intensive glycaemic control has a persistent impact on preventing both microvascular and macrovascular complications long after initiation of the intensified antidiabetic regimen has been discontinued: that is, the 'legacy effect'.
166. Brownlee, M. The pathobiology of diabetic complications: a unifying mechanism. *Diabetes* **54**, 1615–1625 (2005).
A lucid discussion of the molecular pathways involved in the development of diabetic microvascular complications.
167. Giacco, F. & Brownlee, M. Oxidative stress and diabetic complications. *Circ. Res.* **107**, 1058–1070 (2010).
168. Coutinho, M., Gerstein, H. C., Wang, Y. & Yusuf, S. The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. *Diabetes Care* **22**, 233–240 (1999).
169. Taskinen, M.-R. & Borén, J. New insights into the pathophysiology of dyslipidemia in type 2 diabetes. *Atherosclerosis* **239**, 483–495 (2015).
An up-to-date review of the pathogenesis of diabetic dyslipidaemia and its treatment.
170. Isomaa, B. *et al.* Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* **24**, 683–689 (2001).
171. Adler, A. I. *et al.* Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. *BMJ* **321**, 412–419 (2000).
172. Williams, B. Treating hypertension in patients with diabetes: when to start and how low to go? *JAMA* **313**, 573–574 (2015).
The optimal blood pressure goal in hypertensive patients with T2DM is discussed in light of the controversial results observed in the blood pressure arm of the ACCORD trial.
173. Lastra, G., Syed, S., Kurukulasuriya, L. R., Manrique, C. & Sowers, J. R. Type 2 diabetes mellitus and hypertension: an update. *Endocrinol. Metab. Clin. North Am.* **43**, 103–122 (2014).
174. International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. *Diabetes Care* **32**, 1327–1334 (2009).
175. [No authors listed.] Report of the Expert Committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* **20**, 1183–1197 (1997).
A reference publication by the ADA on the diagnosis and classification of diabetes mellitus.
176. Herman, W. H. Diabetes epidemiology: guiding clinical and public health practice: the Kelly West Award Lecture, 2006. *Diabetes Care* **30**, 1912–1919 (2007).
A landmark lecture providing a comprehensive overview of the epidemiology of T2DM and the public health implications for diabetes prevention.
177. DECODE Study Group, European Diabetes Epidemiology Group. Is the current definition for diabetes relevant to mortality risk from all causes and cardiovascular and noncardiovascular diseases? *Diabetes Care* **26**, 688–696 (2003).
178. Engelgau, M. M., Narayan, K. M. & Herman, W. H. Screening for type 2 diabetes. *Diabetes Care* **23**, 1563–1580 (2000).
179. LeFevre, M. L. Behavioral counseling to promote a healthful diet and physical activity for cardiovascular disease prevention in adults with cardiovascular risk factors: U.S. Preventive Services Task Force Recommendation Statement. *Ann. Intern. Med.* **161**, 587–593 (2014).
180. Lindström, J. & Tuomilehto, J. The diabetes risk score: a practical tool to predict type 2 diabetes risk. *Diabetes Care* **26**, 725–731 (2003).

181. Tabaei, B. P. & Herman, W. H. A multivariate logistic regression equation to screen for diabetes: development and validation. *Diabetes Care* **25**, 1999–2003 (2002).
182. World Health Organization. *Definition, diagnosis and classification of diabetes mellitus and its complications. report of a WHO consultation. Part 1: diagnosis and classification of diabetes mellitus* (WHO, 1999).
183. Pan, X. R. *et al.* Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT Diabetes Study. *Diabetes Care* **20**, 537–544 (1997).
184. Knowler, W. C. *et al.* Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N. Engl. J. Med.* **346**, 393–403 (2002).
185. Ramachandran, A. *et al.* The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). *Diabetologia* **49**, 289–297 (2006).
186. Chiasson, J.-L. *et al.* Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* **359**, 2072–2077 (2002).
187. Kawamori, R. *et al.* Voglibose for prevention of type 2 diabetes mellitus: a randomised, double-blind trial in Japanese individuals with impaired glucose tolerance. *Lancet* **373**, 1607–1614 (2009).
188. Knowler, W. C. *et al.* Prevention of type 2 diabetes with troglitazone in the Diabetes Prevention Program. *Diabetes* **54**, 1150–1156 (2005).
189. Gerstein, H. C. *et al.* Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet* **368**, 1096–1105 (2006).
190. Li, G. *et al.* The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. *Lancet* **371**, 1783–1789 (2008).
191. Lindström, J. *et al.* Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. *Lancet* **368**, 1673–1679 (2006).
192. Knowler, W. C. *et al.* 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet* **374**, 1677–1686 (2009).
Long-term follow-up of body weight regain and diabetes incidence in patients with IGT in the Diabetes Prevention Program treated with lifestyle heavy, lifestyle light and metformin, showing that gradual weight regain is the norm and that 40–50% of patients with IGT develop diabetes despite successful weight loss.
193. DeFronzo, R. A., Eldor, R. & Abdul-Ghani, M. Pathophysiologic approach to therapy in patients with newly diagnosed type 2 diabetes. *Diabetes Care* **36**, S127–S138 (2013).
A rational approach to the treatment of T2DM is presented based on its pathophysiology.
194. Raz, I. *et al.* Personalized management of hyperglycemia in type 2 diabetes: reflections from a Diabetes Care Editors' Expert Forum. *Diabetes Care* **36**, 1779–1788 (2013).
195. Nakagami, T., Kawahara, R., Hori, S. & Omori, Y. Glycemic control and prevention of retinopathy in Japanese NIDDM patients. A 10-year follow-up study. *Diabetes Care* **20**, 621–622 (1997).
196. Lim, E. L. *et al.* Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. *Diabetologia* **54**, 2506–2514 (2011).
197. Jazet, I. M. *et al.* Loss of 50% of excess weight using a very low energy diet improves insulin-stimulated glucose disposal and skeletal muscle insulin signalling in obese insulin-treated type 2 diabetic patients. *Diabetologia* **51**, 309–319 (2008).
198. Abdul-Ghani, M. A. *et al.* Initial combination therapy with metformin, pioglitazone and exenatide is more effective than sequential add-on therapy in subjects with new-onset diabetes. Results from the Efficacy and Durability of Initial Combination Therapy for Type 2 Diabetes (EDICT): a randomized trial. *Diabetes Obes. Metab.* **17**, 268–275 (2015).
This prospective randomized trial using a combination of antidiabetic agents proven to reverse known pathophysiological abnormalities in T2DM demonstrated superiority of glycaemic control compared with the stepped approach of metformin followed by a sulfonylurea and then basal insulin recommended by most national diabetes organizations.
199. Harrison, L. B., Adams-Huet, B., Raskin, P. & Lingvay, I. β-cell function preservation after 3.5 years of intensive diabetes therapy. *Diabetes Care* **35**, 1406–1412 (2012).
200. Gram, J. *et al.* Pharmacological treatment of the pathogenetic defects in type 2 diabetes: the randomized multicenter South Danish Diabetes Study. *Diabetes Care* **34**, 27–33 (2011).
201. DeFronzo, R. A. *et al.* Combination of empagliflozin and linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin. *Diabetes Care* **38**, 384–393 (2015).
202. Weng, J. *et al.* Effect of intensive insulin therapy on β-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial. *Lancet* **371**, 1753–1760 (2008).
203. Hu, Y. *et al.* Short-term intensive therapy in newly diagnosed type 2 diabetes partially restores both insulin sensitivity and β-cell function in subjects with long-term remission. *Diabetes Care* **34**, 1848–1853 (2011).
One of several recent studies demonstrating that intensive insulin therapy to correct the decompensated metabolic state in newly diagnosed patients with T2DM can lead to durable glycaemic control without or with a marked reduction in antidiabetic medications.
204. Xiang, A. H. *et al.* Effect of pioglitazone on pancreatic β-cell function and diabetes risk in Hispanic women with prior gestational diabetes. *Diabetes* **55**, 517–522 (2006).
205. Astrup, A. *et al.* Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. *Int. J. Obes. (Lond.)* **36**, 843–854 (2012).
206. Cusi, K., Consoli, A. & DeFronzo, R. A. Metabolic effects of metformin on glucose and lactate metabolism in noninsulin-dependent diabetes mellitus. *J. Clin. Endocrinol. Metab.* **81**, 4059–4067 (1996).
207. Turner, R. C., Cull, C. A., Frighi, V. & Holman, R. R. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. *JAMA* **281**, 2005–2012 (1999).
A landmark UK Prospective Diabetes Study documenting the need for progressive add-on therapies in newly diagnosed patients with T2DM receiving initial therapy with metformin or with a sulfonylurea.
208. Brown, J. B., Conner, C. & Nichols, G. A. Secondary failure of metformin monotherapy in clinical practice. *Diabetes Care* **33**, 501–506 (2010).
209. Kahn, S. E. *et al.* Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N. Engl. J. Med.* **355**, 2427–2443 (2006).
A 5-year ADOPT study demonstrating long-term durable HbA1c reduction with rosiglitazone compared with a progressive rise in HbA1c observed with metformin and sulfonylureas, and a more rapid deterioration of glycaemic control with sulfonylureas compared with metformin.
210. Madiraju, A. K. *et al.* Metformin suppresses gluconeogenesis by inhibiting mitochondrial glycerophosphate dehydrogenase. *Nature* **510**, 542–546 (2014).
211. Ferrannini, E. The target of metformin in type 2 diabetes. *N. Engl. J. Med.* **371**, 1547–1548 (2014).
212. [No authors listed.] Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* **352**, 854–865 (1998).
213. Maedler, K. *et al.* Sulfonylurea induced β-cell apoptosis in cultured human islets. *J. Clin. Endocrinol. Metab.* **90**, 501–506 (2005).
214. Roumie, C. L. *et al.* Comparative effectiveness of sulfonylurea and metformin monotherapy on cardiovascular events in type 2 diabetes mellitus: a cohort study. *Ann. Intern. Med.* **157**, 601–610 (2012).
215. Simpson, S. H., Majumdar, S. R., Tsuyuki, R. T., Eurich, D. T. & Johnson, J. A. Dose–response relation between sulfonylurea drugs and mortality in type 2 diabetes mellitus: a population-based cohort study. *CMAJ* **174**, 169–174 (2006).
216. Simpson, S. H. *et al.* Mortality risk among sulfonylureas: a systematic review and network meta-analysis. *Lancet Diabetes Endocrinol.* **3**, 43–51 (2015).
A review of the published literature that examines the relationship between sulfonylurea therapy and the development of adverse cardiovascular events.
217. Yki-Järvinen, H. Thiazolidinediones. *N. Engl. J. Med.* **351**, 1106–1118 (2004).
218. Eldor, R., DeFronzo, R. A. & Abdul-Ghani, M. *In vivo* actions of peroxisome proliferator-activated receptors: glycemic control, insulin sensitivity, and insulin secretion. *Diabetes Care* **36**, S162–S174 (2013).
An exhaustive review of the mechanism of action, efficacy and side-effect profile of the thiazolidinedione class of antidiabetic medications.
219. Miyazaki, Y., He, H., Mandarino, L. J. & DeFronzo, R. A. Rosiglitazone improves downstream insulin receptor signaling in type 2 diabetic patients. *Diabetes* **52**, 1943–1950 (2003).
220. Gastaldelli, A. *et al.* Thiazolidinediones improve β-cell function in type 2 diabetic patients. *Am. J. Physiol. Endocrinol. Metab.* **292**, E871–E883 (2007).
221. DeFronzo, R. A. *et al.* Prevention of diabetes with pioglitazone in ACT NOW: physiologic correlates. *Diabetes* **62**, 3920–3926 (2013).
222. Kahn, S. E. *et al.* Effects of rosiglitazone, glyburide, and metformin on β-cell function and insulin sensitivity in ADOPT. *Diabetes* **60**, 1552–1560 (2011).
223. Dormandy, J. A. *et al.* Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* **366**, 1279–1289 (2005).
A large prospective study (PROactive) demonstrating that pioglitazone significantly reduced the second principal end point of myocardial infarction, stroke and cardiovascular death; the primary end point did not reach statistical significance because of the inclusion of peripheral arterial disease and leg revascularization, which is known to be refractory to medical intervention, including statin therapy.
224. Aronoff, S. *et al.* Pioglitazone hydrochloride monotherapy improves glycemic control in the treatment of patients with type 2 diabetes: a 6-month randomized placebo-controlled dose-response study. The Pioglitazone 001 Study Group. *Diabetes Care* **23**, 1605–1611 (2000).
225. Erdmann, E., Song, E., Spanheimer, R., van Troostenburg de Bruyn, A.-R. & Perez, A. Observational follow-up of the PROactive study: a 6-year update. *Diabetes Obes. Metab.* **16**, 63–74 (2014).
226. [No authors listed.] Takeda announces completion of the post-marketing commitment to submit data to the FDA, the EMA and the PMDA for pioglitazone containing medicines including ACTOS. *Takeda* [online], http://www.takeda.us/newsroom/press_release_detail.aspx?year=2014&id=314 (2014).
227. Levin, D. *et al.* Pioglitazone and bladder cancer risk: a multipopulation pooled, cumulative exposure analysis. *Diabetologia* **58**, 493–504 (2015).
228. Kjems, L. L., Holst, J. J., Vølund, A. & Madsbad, S. The influence of GLP-1 on glucose-stimulated insulin secretion: effects on β-cell sensitivity in type 2 and nondiabetic subjects. *Diabetes* **52**, 380–386 (2003).
229. Vilsbøll, T., Krarup, T., Madsbad, S. & Holst, J. J. Defective amplification of the late phase insulin response to glucose by GIP in obese Type II diabetic patients. *Diabetologia* **45**, 1111–1119 (2002).
230. Aroda, V. R. *et al.* Efficacy of GLP-1 receptor agonists and DPP-4 inhibitors: meta-analysis and systematic review. *Clin. Ther.* **34**, 1247–1258.e22 (2012).
231. Deacon, C. F. Dipeptidyl peptidase-4 inhibitors in the treatment of type 2 diabetes: a comparative review. *Diabetes Obes. Metab.* **13**, 7–18 (2011).
232. Balas, B. *et al.* The dipeptidyl peptidase IV inhibitor vildagliptin suppresses endogenous glucose production and enhances islet function after single-dose administration in type 2 diabetic patients. *J. Clin. Endocrinol. Metab.* **92**, 1249–1255 (2007).
233. Drucker, D. J. Incretin action in the pancreas: potential promise, possible perils, and pathological pitfalls. *Diabetes* **62**, 3316–3323 (2013).
A comprehensive review of the effect of incretin hormones on pancreatic hormone secretion and pathology by one of the world's leading authorities.
234. White, W. B. *et al.* Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N. Engl. J. Med.* **369**, 1327–1335 (2013).

235. Scirica, B. M. *et al.* Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N. Engl. J. Med.* **369**, 1317–1326 (2013).
236. Cervera, A. *et al.* Mechanism of action of exenatide to reduce postprandial hyperglycemia in type 2 diabetes. *Am. J. Physiol. Endocrinol. Metab.* **294**, E846–E852 (2008).
237. Bunck, M. C. *et al.* Effects of exenatide on measures of β-cell function after 3 years in metformin-treated patients with type 2 diabetes. *Diabetes Care* **34**, 2041–2047 (2011).
A landmark 3-year prospective study demonstrating the marked and durable improvement in β-cell function using the combined hyperglycaemic and euglycaemic insulin clamp techniques following exenatide treatment in patients with T2DM.
238. Klonoff, D. C. *et al.* Exenatide effects on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type 2 diabetes treated for at least 3 years. *Curr. Med. Res. Opin.* **24**, 275–286 (2008).
239. Schwartz, S. & Kohl, B. A. Type 2 diabetes mellitus and the cardiometabolic syndrome: impact of incretin-based therapies. *Diabetes Metab. Syndr. Obes.* **3**, 227–242 (2010).
240. Eng, C., Kramer, C. K., Zinman, B. & Retnakaran, R. Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis. *Lancet* **384**, 2228–2234 (2014).
241. Egan, A. G. *et al.* Pancreatic safety of incretin-based drugs — FDA and EMA assessment. *N. Engl. J. Med.* **370**, 794–797 (2014).
242. Van de Laar, F. A. *et al.* Alpha-glucosidase inhibitors for type 2 diabetes mellitus. *Cochrane Database Syst. Rev.* **2**, CD003639 (2005).
243. Esposito, K. *et al.* Dipeptidyl peptidase-4 inhibitors and HbA1c target of < 7% in type 2 diabetes: meta-analysis of randomized controlled trials. *Diabetes Obes. Metab.* **13**, 594–603 (2011).
244. Richter, B., Bandeira-Echtler, E., Bergerhoff, K. & Lerch, C. L. Dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes mellitus. *Cochrane Database Syst. Rev.* **2**, CD006739 (2008).
245. Abdul-Ghani, M. A., Norton, L. & DeFronzo, R. A. Role of sodium-glucose cotransporter 2 (SGLT 2) inhibitors in the treatment of type 2 diabetes. *Endocr. Rev.* **32**, 515–531 (2011).
An excellent review of the mechanism of action, efficacy and safety of the recently approved SGLT2 inhibitor class of antidiabetic medications.
246. Wright, E. M., Loo, D. D. & Hirayama, B. A. Biology of human sodium glucose transporters. *Physiol. Rev.* **91**, 733–794 (2011).
247. Merovci, A. *et al.* Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production. *J. Clin. Invest.* **124**, 509–514 (2014).
248. Ferrannini, E. *et al.* Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. *J. Clin. Invest.* **124**, 499–508 (2014).
249. Abdul-Ghani, M. A., DeFronzo, R. A. & Norton, L. Novel hypothesis to explain why SGLT2 inhibitors inhibit only 30–50% of filtered glucose load in humans. *Diabetes* **62**, 3324–3328 (2013).
250. Cherney, D. Z. I. *et al.* Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. *Circulation* **129**, 587–597 (2014).
251. Holman, R. R. *et al.* Three-year efficacy of complex insulin regimens in type 2 diabetes. *N. Engl. J. Med.* **361**, 1736–1747 (2009).
A comparison of the efficacy and side-effect profile of commonly used complex insulin regimens for the treatment of patients with T2DM.
252. Gough, S. C. L. *et al.* Efficacy and safety of a fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with its components given alone: results of a phase 3, open-label, randomised, 26-week, treat-to-target trial in insulin-naive patients with type 2 diabetes. *Lancet Diabetes Endocrinol.* **2**, 885–893 (2014).
253. Wilding, J. P. *et al.* Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin: a randomized trial. *Ann. Intern. Med.* **156**, 405–415 (2012).
254. Anderson, M., Powell, J., Campbell, K. M. & Taylor, J. R. Optimal management of type 2 diabetes in patients with increased risk of hypoglycemia. *Diabetes Metab. Syndr. Obes.* **7**, 85–94 (2014).
255. Schopman, J. E. *et al.* The incidence of mild and severe hypoglycaemia in patients with type 2 diabetes mellitus treated with sulfonylureas: a systematic review and meta-analysis. *Diabetes Metab. Res. Rev.* **30**, 11–22 (2014).
256. Desouza, C., Salazar, H., Cheong, B., Murgo, J. & Fonseca, V. Association of hypoglycemia and cardiac ischemia: a study based on continuous monitoring. *Diabetes Care* **26**, 1485–1489 (2003).
257. Gerstein, H. C. *et al.* Effects of intensive glucose lowering in type 2 diabetes. *N. Engl. J. Med.* **358**, 2545–2559 (2008).
The ORIGIN trial demonstrated that physiological insulin replacement doses (30–40 units per day) in newly diagnosed patients with T2DM could control HbA1c without an increased risk of cardiovascular events; however, the risk of hypoglycaemia was significantly increased, and the study did not examine the effect of higher doses of insulin, which are usually required to normalize glycaemia in more long-standing diabetes, on cardiovascular risk or other potential side effects of insulin therapy.
258. Cushman, W. C. *et al.* Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N. Engl. J. Med.* **362**, 1575–1585 (2010).
259. James, P. A. *et al.* 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* **311**, 507–520 (2014).
260. Emdin, C. *et al.* Association of cardiovascular trial registration with positive study findings: Epidemiological Study of Randomized Trials (ESORT). *JAMA Intern. Med.* **175**, 304–307 (2015).
261. Testa, M. A. & Simonson, D. C. Health economic benefits and quality of life during improved glycemic control in patients with type 2 diabetes mellitus: a randomized, controlled, double-blind trial. *JAMA* **280**, 1490–1496 (1998).
This was the first randomized trial to demonstrate that better glucose control improves QOL, cognitive function and general perceived health, and reduces symptom distress and absenteeism from work.
262. Testa, M. A. & Simonson, D. C. Assesment of quality-of-life outcomes. *N. Engl. J. Med.* **334**, 835–840 (1996).
263. Testa, M. A., Simonson, D. C. & Turner, R. R. Valuing quality of life and improvements in glycemic control in people with type 2 diabetes. *Diabetes Care* **21**, C44–C52 (1998).
264. Bode, B. W. *et al.* Patient-reported outcomes following treatment with the human GLP-1 analogue liraglutide or glimepiride in monotherapy: results from a randomized controlled trial in patients with type 2 diabetes. *Diabetes Obes. Metab.* **12**, 604–612 (2010).
265. Testa, M. A. *et al.* Comparative effectiveness of basal-bolus versus premix analog insulin on glycemic variability and patient-centered outcomes during insulin intensification in type 1 and type 2 diabetes: a randomized, controlled, crossover trial. *J. Clin. Endocrinol. Metab.* **97**, 3504–3514 (2012).
This randomized trial demonstrated that patient satisfaction with treatment was more positively affected by improved QOL, reduced glucose variability and better glycaemic control with a basal-bolus regimen than negatively affected by the burden of additional injections.
266. Cotter, A. P., Durant, N., Agne, A. A. & Cherrington, A. L. Internet interventions to support lifestyle modification for diabetes management: a systematic review of the evidence. *J. Diabetes Complications* **28**, 243–251 (2014).
267. Rose, M. *et al.* The PROMIS Physical Function item bank was calibrated to a standardized metric and shown to improve measurement efficiency. *J. Clin. Epidemiol.* **67**, 516–526 (2014).
268. DeFronzo, R. A. & Triplitt, C. Novel agents for T2DM. *Diabetes Spectr.* **27**, 100–112 (2014).
This article presents a more detailed review of novel antidiabetic agents that currently are being investigated in animals and humans for the treatment of T2DM.
269. Wong, A. K., Howie, J., Petrie, J. R. & Lang, C. C. AMP-activated protein kinase pathway: a potential therapeutic target in cardiometabolic disease. *Clin. Sci. (Lond.)* **116**, 607–620 (2009).
270. Agrawal, N. K. & Kant, S. Targeting inflammation in diabetes: newer therapeutic options. *World J. Diabetes* **5**, 697–710 (2014).
Inflammation in insulin target tissues and β-cells is a now well-established pathogenetic abnormality T2DM. This article reviews the mechanism by which inflammation contributes to glucose intolerance in T2DM and potential interventions to suppress inflammation and improve insulin sensitivity and β-cell function.
271. Poy, M. N. *et al. miR-375* maintains normal pancreatic α- and β-cell mass. *Proc. Natl Acad. Sci. USA* **106**, 5813–5818 (2009).
272. Burant, C. F. *et al.* TAK-875 versus placebo or glimepiride in type 2 diabetes mellitus: a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet* **379**, 1403–1411 (2012).
273. Assmann, A., Hinault, C. & Kulkarni, R. N. Growth factor control of pancreatic islet regeneration and function. *Pediatr. Diabetes* **10**, 14–32 (2009).
274. Vasavada, R. C. *et al.* Protein kinase C-ζ activation markedly enhances β-cell proliferation: an essential role in growth factor mediated β-cell mitogenesis. *Diabetes* **56**, 2732–2743 (2007).
275. Wiederkehr, A. & Wollheim, C. B. Mitochondrial signals drive insulin secretion in the pancreatic β-cell. *Mol. Cell. Endocrinol.* **353**, 128–137 (2012).
276. Wang, C. *et al.* Deficiency of APPL1 in mice impairs glucose-stimulated insulin secretion through inhibition of pancreatic beta cell mitochondrial function. *Diabetologia* **56**, 1999–2009 (2013).
277. Sivitz, W. I. & Yorek, M. A. Mitochondrial dysfunction in diabetes: from molecular mechanisms to functional significance and therapeutic opportunities. *Antioxid. Redox Signal.* **12**, 537–577 (2010).
278. Li, N., Stojanovski, S. & Maechler, P. Mitochondrial hormesis in pancreatic β cells: does uncoupling protein 2 play a role? *Oxid. Med. Cell. Longev.* **2012**, 740849 (2012).
279. Aquilano, K., Baldelli, S., Pagliei, B. & Ciriolo, M. R. Extranuclear localization of SIRT1 and PGC-1α: an insight into possible roles in diseases associated with mitochondrial dysfunction. *Curr. Mol. Med.* **13**, 140–154 (2013).
280. Matschinsky, F. M. *et al.* Glucokinase activators for diabetes therapy: May 2010 status report. *Diabetes Care* **34**, S236–S243 (2011).
281. Engel, S. S. Glycemic and lipid effects of the short-acting glucagon receptor antagonist MK-3577 in patients with type 2 diabetes. *Diabetes Abstr.* **61**, A266 (2012).
282. Gumbiner, B. Pronounced glucose (G) reduction in poorly controlled T2DM with MB07803, a novel fructose-1, 6-biphosphatase inhibitor (FBPasel) with reduced potential for acid-base disturbance versus the 1st generation FBPasel CS-917. *Diabetes Abstr.* **58**, LB4 (2009).
283. Kumashiro, N. *et al.* Targeting pyruvate carboxylase reduces gluconeogenesis and adiposity and improves insulin resistance. *Diabetes* **62**, 2183–2194 (2013).
284. Stark, R. *et al.* A role for mitochondrial phosphoenolpyruvate carboxykinase (PEPCK-M) in the regulation of hepatic gluconeogenesis. *J. Biol. Chem.* **289**, 7257–7263 (2014).
285. Harlan, D. M., Kenyon, N. S., Korsgren, O. & Roep, B. O. Current advances and travails in islet transplantation. *Diabetes* **58**, 2175–2184 (2009).
286. Motté, E. *et al.* Composition and function of macroencapsulated human embryonic stem cell-derived implants: comparison with clinical human islet cell grafts. *Am. J. Physiol. Endocrinol. Metab.* **307**, E838–E846 (2014).
287. Pagliuca, F. W. *et al.* Generation of functional human pancreatic β cells *in vitro*. *Cell* **159**, 428–439 (2014).
288. Blum, B. *et al.* Reversal of β cell de-differentiation by a small molecule inhibitor of the TGFβ pathway. *eLife* **3**, e02809 (2014).
289. Pickup, J. C. Banting Memorial Lecture 2014* Technology and diabetes care: appropriate and personalized. *Diabet. Med.* **32**, 3–13 (2015).
290. Peyser, T., Dassau, E., Breton, M. & Skyler, J. S. The artificial pancreas: current status and future prospects in the management of diabetes. *Ann. NY Acad. Sci.* **1311**, 102–123 (2014).
This article presents an up-to-to-date status report on progress with the artificial pancreas (closed-loop system).
291. Klonoff, D. C. Afrezza inhaled insulin: the fastest-acting FDA-approved insulin on the market has favorable properties. *J. Diabetes Sci. Technol.* **8**, 1071–1073 (2014).

292. Eldor, R., Arbit, E., Corcos, A. & Kidron, M. Glucose-reducing effect of the ORMD-0801 oral insulin preparation in patients with uncontrolled type 1 diabetes: a pilot study. *PLoS ONE* **8**, e59524 (2013).
293. DeFronzo, R. A. Dissociation between metformin plasma exposure and its glucose-lowering effect: a novel gut-mediated mechanism of action. *Diabetes* **62**, a281 (2013).
294. DePaoli, A. M., Higgins, L. S., Henry, R. R., Mantzoros, C. & Dunn, F. L. Can a selective PPARγ modulator improve glycemic control in patients with type 2 diabetes with fewer side effects compared with pioglitazone? *Diabetes Care* **37**, 1918–1923 (2014).
295. Colca, J. R., Tanis, S. P., McDonald, W. G. & Kletzien, R. F. Insulin sensitizers in 2013: new insights for the development of novel therapeutic agents to treat metabolic diseases. *Expert Opin. Investig. Drugs* **23**, 1–7 (2014).
296. Suh, J. M. *et al.* Endocrinization of FGF1 produces a neomorphic and potent insulin sensitizer. *Nature* **513**, 436–439 (2014).
297. Gaich, G. *et al.* The effects of LY2405319, an FGF21 analog, in obese human subjects with type 2 diabetes. *Cell Metab.* **18**, 333–340 (2013).
298. Jeoung, N. H. & Harris, R. A. Role of pyruvate dehydrogenase kinase 4 in regulation of blood glucose levels. *Korean Diabetes J.* **34**, 274–283 (2010).
299. Povel, C. M. *et al.* Metabolic syndrome model definitions predicting type 2 diabetes and cardiovascular disease. *Diabetes Care* **36**, 362–368 (2013).
300. Pacini, G., Mari, A., Fouqueray, P., Bolze, S. & Roden, M. Imeglimin increases glucose-dependent insulin secretion and improves β-cell function in patients with type 2 diabetes. *Diabetes Obes. Metab.* **17**, 541–545 (2015).
301. Birch, A. M., Buckett, L. K. & Turnbull, A. V. DGAT1 inhibitors as anti-obesity and anti-diabetic agents. *Curr. Opin. Drug Discov. Devel.* **13**, 489–496 (2010).
302. Liu, L. *et al.* Upregulation of myocellular DGAT1 augments triglyceride synthesis in skeletal muscle and protects against fat-induced insulin resistance. *J. Clin. Invest.* **117**, 1679–1689 (2007).
303. Harrima, G., Greenwood, J. & Bhar, S. Acetyl-CoA carboxylase inhibition by NDI-630 inhibits fatty acid synthesis stimulates fatty acid oxidative, reduces body weight, improvise insulin sensitivity, and modulates dyslipidemia in rats. *Diabetes Abstr.* **62**, A161 (2013).
304. Tao, H., Zhang, Y., Zeng, X., Shulman, G. I. & Jin, S. Niclosamide ethanolamine-induced mild mitochondrial uncoupling improves diabetic symptoms in mice. *Nat. Med.* **20**, 1263–1269 (2014).
305. Perry, R. J. *et al.* Reversal of hypertriglyceridemia, fatty liver disease, and insulin resistance by a liver-targeted mitochondrial uncoupler. *Cell Metab.* **18**, 740–748 (2013).
306. Garvey, W. T. *et al.* Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study. *Am. J. Clin. Nutr.* **95**, 297–308 (2012).
307. Carlsson, L. M. *et al.* Bariatric surgery and prevention of type 2 diabetes in Swedish obese subjects. *N. Engl. J. Med.* **367**, 695–704 (2012).
The effectiveness and safety of bariatric surgery in the treatment of obesity and T2DM is reviewed in this longest ongoing study on surgical intervention.
308. Neuschwander-Tetri, B. A. *et al.* Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. *Lancet* **385**, 956–965 (2014).
309. Out, C., Groen, A. K. & Brufau, G. Bile acid sequestrants: more than simple resins. *Curr. Opin. Lipidol.* **23**, 43–55 (2012).
310. Cellitti, S. A novel GLP-1-FGF21 fusion protein for the treatment of diabetes and obesity. *Keystone Symp. Obes.* (2014).
311. Thareja, S., Aggarwal, S., Bhardwaj, T. R. & Kumar, M. Protein tyrosine phosphatase 1B inhibitors: a molecular level legitimate approach for the management of diabetes mellitus. *Med. Res. Rev.* **32**, 459–517 (2012).
312. Chakraborty, C., Doss, C. G., Bandyopadhyay, S. & Agoramoorthy, G. Influence of miRNA in insulin signaling pathway and insulin resistance: micro-molecules with a major role in type-2 diabetes. *Wiley Interdiscip. Rev. RNA* **5**, 697–712 (2014).
313. Tilg, H. & Moschen, A. R. Microbiota and diabetes: an evolving relationship. *Gut* **63**, 1513–1521 (2014).
314. Patel, S. R., Hakim, D., Mason, J. & Hakim, N. The duodenal–jejunal bypass sleeve (EndoBarrier Gastrointestinal Liner) for weight loss and treatment of type 2 diabetes. *Surg. Obes. Relat. Dis.* **9**, 482–484 (2013).
315. Bhatt, M. P., Lim, Y.-C. & Ha, K.-S. C-peptide replacement therapy as an emerging strategy for preventing diabetic vasculopathy. *Cardiovasc. Res.* **104**, 234–244 (2014).
316. Bhat, M., Pouliot, M., Couture, R. & Vaucher, E. The kallikrein–kinin system in diabetic retinopathy. *Prog. Drug Res.* **69**, 111–143 (2014).
317. Hajhosseiny, R. *et al.* Have we reached the limits for the treatment of diabetic nephropathy? *Expert Opin. Investig. Drugs* **23**, 511–522 (2014).
318. Williams, M. E. *et al.* Effects of pyridoxamine in combined phase 2 studies of patients with type 1 and type 2 diabetes and overt nephropathy. *Am. J. Nephrol.* **27**, 605–614 (2007).
319. De Zeeuw, D. *et al.* The endothelin antagonist atrasentan lowers residual albuminuria in patients with type 2 diabetic nephropathy. *J. Am. Soc. Nephrol.* **25**, 1083–1093 (2014).
320. Boussageon, R. *et al.* Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials. *BMJ* **343**, d4169 (2011).
321. Colditz, G. A., Willett, W. C., Rotnitzky, A. & Manson, J. E. Weight gain as a risk factor for clinical diabetes mellitus in women. *Ann. Intern. Med.* **122**, 481–486 (1995).
322. Chan, J. M., Rimm, E. B., Colditz, G. A., Stampfer, M. J. & Willett, W. C. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. *Diabetes Care* **17**, 961–969 (1994).

Acknowledgements
The authors acknowledge grants from: the South Texas Veterans Healthcare System to R.A.D.; the National Institutes of Health (grants R01DK24092 to R.A.D.; DK58845 and P30 DK46200 to F.B.H.; R01 DK-040936, R01 DK-049230, R24 DK-085836, UL1 RR-045935, R01 DK-082659 and R24 DK085610 to G.I.S.; P30 DK036836 to C.R.K. Novo Nordisk Foundation for Basic Metabolic Research and the University of Copenhagen to G.I.S. and C.R.K.; DVA-Merit Review grant and VA San Diego Healthcare System to R.H.; National Institute for Diabetes and Digestive and Kidney Disease (grant P30DK092926) to W.H.; the Swedish Research Council (grants 2010–3490 and 2008–6589) and European Council (grants GA269045) to L.G.; Italian Ministry of University & Research (MIUR 2010329EKE) to E.F.; the Patient-Centered Outcomes Research Institute (PCORI) Program Award (CE1304-6756) to D.C.S. and M.A.T.; NovoNordisk Foundation to the NNF Center for Basic Metabolic Research to J.H. W.H. acknowledges the Michigan Center for Diabetes Translational Research and I.R. thanks R. Sprung for editorial assistance.

Author contributions
Introduction (R.R.H.); Epidemiology (F.B.H.); Mechanisms/pathophysiology (L.C.G., C.R.K., E.F., G.I.S. and R.A.D.); Diagnosis, screening and prevention (W.H.H.); Management (R.A.D.); Quality of life (D.C.S. and M.A.T.); Outlook (I.R., J.J.H. and R.W.); overview of Primer (R.A.D.).

Competing interests
The authors declare the following potential COI: (1) R.A.D.: Research Grant Support - AstraZeneca, Bristol Myers Squibb, Janssen; Speakers Bureau - AstraZeneca, Novo Nordisk, Advisory Board/Consultant - AstraZeneca, Janssen, Novo Nordisk, Boehringer Ingelheim, Lexicon, Intarcia; (2) E.F.: Research Grant Support - Boehringer Ingelheim, Eli Lilly; Consultant/Speaker Bureau-Boehringer Ingelheim, Eli Lilly, Sanofi, Novo Nordisk, Janssen, AstraZeneca, Takeda, Medtronic, Intarcia; (3) C.R.K. serves as a consultant for Medimmune, Merck, Five Prime Therapeutics, CohBar, Antriabio, and Catabasis; (4) L.G. has no conflict of interest; (5) R.H. has received grant support from Hitachi, Janssen, Eli Lilly, Sanofi-Aventis and Viacyte and is a consultant/advisory board member for Alere, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Clin Met, Eisai, Elcelyx, Gilead, Intarcia, Isis, Janssen, Merck, Novo Nordisk, Sanofi-Aventis, and Vivus; (6) W.H.H. has no conflict of interest; (7) J.J.H. has received grant support from Novartis and Merck and is a consultant/advisory board member for Glaxo, Smith, Kline, Novo Nordisk, and Zealand Pharmaceuticals; (8) M.A.T. has no conflict of interest; (9) R.W. serves as a consultant for Medtronics and Kamada and is on the speaker's bureau for Medtronics and Novo Nordisk; (10) F.H. has received research support from California Walnut Commission and Metegenics; (11) G.I.S. serves on scientific advisory boards for Merck and Novartis and he has received research grant support from Gilead Pharmaceuticals; (12) D.C.S. has no conflict of interest; (13) I.R. – Advisory Board: Novo Nordisk, Astra Zeneca/BMS, MSD, Eli Lilly, Sanofi, Medscape Cardiology; Consultant: Astra Zeneca/BMS, Insuline; Speaker's Bureau: Eli Lilly, Novo Nordisk, Astra Zeneca/BMS, J&J, Sanofi, MSD, Novartis, Teva; Shareholder: Insuline, Labstyle.