Treatment of type 2 diabetes: challenges, hopes, and anticipated successes

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Despite the successful development of new therapies for the treatment of type 2 diabetes, such as glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose cotransporter-2 inhibitors, the search for novel treatment options that can provide better glycaemic control and at reduce complications is a continuous effort. The present Review aims to present an overview of novel targets and mechanisms and focuses on glucose-lowering effects guiding this search and developments. We discuss not only novel developments of insulin therapy (eg, so-called smart insulin preparation with a glucose-dependent mode of action), but also a group of drug classes for which extensive research efforts have not been rewarded with obvious clinical impact. We discuss the potential clinical use of the salutary adipokine adiponectin and the hepatokine fibroblast growth factor (FGF) 21, among others. A GLP-1 peptide receptor agonist (semaglutide) is now available for oral absorption, and small molecules activating GLP-1 receptors appear on the horizon. Bariatric surgery and its accompanying changes in the gut hormonal milieu offer a background for unimolecular peptides interacting with two or more receptors (for GLP-1, glucose-dependent insulinotropic polypeptide, glucagon, and peptide YY) and provide more substantial glycaemic control and bodyweight reduction compared with selective GLP-1 receptor agonists. These and additional approaches will help expand the toolbox of effective medications needed for optimising the treatment of well delineated subgroups of type 2 diabetes or help develop personalised approaches for glucose-lowering drugs based on individual characteristics of our patients.

Lancet Diabetes Endocrinol 2021; 9: 525–44

Published Online June 25, 2021 https://doi.org/10.1016/S2213-8587(21)00113-3

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Introduction

Diabetes is a chronic disease characterised by hyperglycaemia, ultimately leading to microvascular (retinopathy, nephropathy, neuropathy) damage and to macrovascular (atherosclerotic ischaemic) events like myocardial infarction, cerebrovascular insults, and complications related to peripheral vascular disease, including the diabetic foot syndrome. The risk for neoplastic diseases is also increased in people with diabetes. Although the development of complications is higher in patients with associated obesity, arterial hypertension, lipid disorders, and a variety of other risk factors, it is also determined by glycaemic control (ie, the quantitative impact of exposure to high plasma glucose concentrations over a long period). Glucose-lowering therapy, therefore, remains a mainstay of diabetes management, in conjunction with a healthy lifestyle and with other medications specifically addressing the prevention or therapy of diabetes-related complications.

The number of patients with diabetes and its proportion relative to the overall population is rising worldwide, and despite the development of numerous and quite successful novel treatment approaches (eg, continuous glucose monitoring, insulin pumps, sodium-glucose co-transporter-2 [SGLT2] inhibitors, glucagon-like peptide-1 [GLP-1] receptor agonists), the fraction of patients with well controlled diabetes has not risen as hoped for. This situation might in part be related to limited access (eg, high costs and lack of reimbursement by insurance policies), insufficient education of patients regarding the need for glycaemic control, and other reasons for so-called therapeutic inertia. However, it could hopefully be overcome by improving the glucose-lowering efficacy of future diabetes medications, and by addressing mechanisms associated with fewer and less severe adverse drug effects (weight gain, hypoglycaemia, and others). The search for new diabetes drugs undoubtedly is an active area of research and development. Directions, activities, hopes, successes, and disappointments related to the search for new and better glucose-lowering medications have been excellently summarised in the past.[1–4] The purpose of the present Review is to present an updated account of promising avenues, hopefully leading to more efficacious and better tolerable glucose-lowering medications or treatment approaches, with a focus on type 2 diabetes. Our strategy has been to focus on developments which have already yielded promising results from published phase 1 or phase 2a studies, but we also mention earlier proof-of-principle findings that suggest a high likelihood of future success. Furthermore, we mainly refer to glucose-lowering approaches to treat type 2 diabetes, however being aware that the aim finally is to prevent diabetic complications, and that strategies to directly address cardiovascular, renal, and other complications related to type 2 diabetes might gain more impact in future years. So far, the important cardiorenal protective classes, GLP-1 receptor agonists and SGLT-2 inhibitors, were initially developed because of their glucose-lowering potential. Further attempts to directly address other risk factors typically associated with type 2 diabetes (obesity, arterial hypertension, atherogenic lipoproteins, etc) will only be discussed if they play a role as corollary of glucose-lowering approaches.

Innovations in insulin preparations and therapy

Even 100 years after the first clinical use of insulin, activities are underway to further optimise insulin therapy by improving insulin preparations, injection devices, and efficacy and safety outcomes.[5] Since some of

See Online for appendix

the approaches are relevant for both type 1 and type 2 diabetes, we refer to the appendix (pp 1–6) for a summary of current developments. Here, we focus on innovations mainly relevant for patients with type 2 diabetes.

Insulin icodec is a novel basal insulin analogue, which (like insulin detemir and insulin degludec) has a prolonged action profile due to a free fatty acid side chain promoting binding to albumin.[6,7] The pharmacokinetic profile makes insulin icodec suitable for once-weekly subcutaneous administration.[6,7] In a head-to-head comparison with insulin glargine in insulin-naive patients with type 2 diabetes allowing titration of insulin once a week, after 26 weeks, a mean HbA_{1c} of 6·7% (baseline 8·1%) was achieved with insulin icodec, which was slightly, but not significantly, lower than the 6·9% (baseline 8·0%) reached with insulin glargine.[8] Reductions in fasting plasma glucose, changes in bodyweight, and incidences of (clinically significant or severe) hypoglycaemic episodes were not significantly different between treatments with insulin icodec or glargine.[8] Variations in fasting plasma glucose throughout a week (ie, between injections) has not been reported. There are other developments of once-weekly injected insulin preparations, which use insulin fused to Fc fragments of immunoglobulins, like ^{LAPS}insulin115[9] or LY3209590 (basal insulin Fc, NCT03736785), however, at earlier stages.

Other developments (eg, oral insulin preparations, small molecular insulin receptor activators, devices facilitating the oral administration of insulin for enteral absorption and portal delivery) are presented in the appendix (pp 1–6).

Additional research efforts aim at generating a glucose-responsive supply of insulin (so-called smart insulins), either by introducing elements of glucose responsiveness to the elimination of insulin from the circulation (faster, when glucose concentrations are low), or to the absorption of insulin from (subcutaneous) depots. The former approach led to the development of MK-2640, which is an insulin analogue conjugated with a saccharide.[10] This insulin saccharide conjugate can interact with the insulin receptor, but also can bind to mannose receptor C type 1, which is expressed on macrophages, Kupffer cells, and hepatic sinusoidal endothelial cells, and will facilitate its elimination. Glucose will compete with the insulin saccharide conjugate for binding to mannose receptor C type 1, so that at hyperglycaemia, less MK-2640 will be eliminated from the circulation.[10] Indeed, in dogs, the clearance of such an insulin saccharide conjugate (highly similar to MK-2640) increased by 23% with plasma glucose clamped at 80 mg/dL versus 240 mg/dL.[11] Nevertheless, the development had to be given up, because in human patients, the capacity of the mannose receptor C type 1 for binding and facilitating the clearance of insulin saccharide conjugates was saturable already at doses in the range relevant for diabetes treatment.[12]

Glucose-dependent absorption from subcutaneous insulin depots has been achieved using different approaches. Two of them are illustrated in figure 1. The first approach (smart insulin A in figure 1) relies on the self-assembly of glucose-responsive vesicles (nanoparticles) composed of insulin and the enzyme glucose oxidase in the core, 2-nitroimidazole (hydrophobic), and 2-aminoimidazole (hydrophilic, inner shell), and hypoxia-sensitive hyaluronic acid (outer shell). High tissue glucose concentrations lead to oxygen consumption mediated by the enzyme glucose oxidase, which will trigger dissociation of the glucose-responsive vesicles and, thus, the release of insulin.[13] These glucose-responsive vesicles are administered as microneedle-containing patches painlessly penetrating the skin to deliver their insulin content into subcutaneous adipose tissue. Similar approaches make use of the H_2O_2 generated by glucose oxidase, employing phenylboronic acid pinacol ester as a H_2O_2-sensitive block as part of a triblock co-polymer also containing polyethylene glycol and phenyl boronic acid as a glucose-sensitive block.[15] H_2O_2 will catalyse breaks in phenylboronic acid pinacol ester and prompt release of insulin.[15] Similar approaches with different chemical excipients have also been described.[16]

The second approach (smart insulin B in figure 1) makes use of phenylboronic acid and its capacity to complex with 1,2 and 1,3-*cis*-diols, as found in carbohydrates, to form boronate esters. A nanogel containing these components and an amphiphilic acrylamide gel backbone will, at low glucose concentrations, form a skin layer around the gel particles, which prevents insulin release.[14] At high glucose concentrations, phenylboronic acid will complex with glucose to be negatively charged, which will be hydrated to resolve the skin layer, allowing insulin release.[14]

All methods described above lead to an insulin release, which, after an initial delay, is proportional to the ambient glucose concentrations, and is maintained at a relatively constant level for prolonged periods.[13–16] Furthermore, alternating periods with high and low glucose concentrations lead to appropriate changes in insulin release without much delay,[13,14,16] proving the viability of these approaches to provide glucose-responsive release of insulin. Such systems will clearly help tailoring the insulin provision to the current (rapidly changing) needs, thus potentially improving efficacy and avoiding hypoglycaemia. One should be aware that these smart insulin developments are still at an early stage.

Pharmaceutical therapeutic approaches with limited probability of success

In this paragraph, we want to summarise developments, which have often been mentioned in past reviews of promising novel drugs for type 2 diabetes,[1–4] but for which latest scientific support does not indicate a high probability of yielding approved medications with a convincing benefit–risk relationship. Some information on clinical results of employing peroxisome-proliferator receptor agonists (PPARs), glucagon-receptor agonists, glucokinase activators, and 11 β-hydroxysteroid dehydrogenase inhibitors are summarised in table 1.

PPAR agonists

More than 20 years ago, the thiazolidinediones pioglitazone and rosiglitazone were approved for the treatment of type 2 diabetes, promising a substantial effect on the associated cardiovascular burden due to their principal effects on insulin resistance, which was believed to play a central role in the pathogenesis of macroangiopathic complications. Cardiovascular outcomes studies with pioglitazone, providing questionable[17] or more convincing evidence[18] for substantial benefits, while at the same time delineating risks for worsening oedema,[17,18] heart failure,[17] and bone fractures[17,18,36] lead to a more cautious and less widespread use.[37] It has not been clarified, whether use of lower doses will reduce these adverse outcomes, while preserving potential benefits. Nevertheless, novel PPARγ (eg, lobeglitazone)[38,39] or PPAR pan agonists (eg, chiglitazar)[40,41] continue to be developed. However, clinical trials with lobeglitazone, some of which were performed head-to-head against pioglitazone, do not suggest important differences regarding glycaemic effects and adverse events.[38,42] However, lobeglitazone might have more pronounced effects on albuminuria as compared with pioglitazone.[38] Cardiovascular outcomes studies are not available for these novel PPAR agonists.

PPARγ/$_{\delta}$ coagonists like elafibranor have been tested in patients with steatohepatitis, of whom 40% had type 2 diabetes.[43] Apart from beneficial effects on liver histology, HbA_{1c} was reduced by 0·5% with 120 mg per day of elafibranor. In addition, there were strong trends towards a reduction in fasting plasma glucose, insulin and C-peptide concentrations, insulin resistance, and free fatty acids for the subgroup with type 2 diabetes.[43] In addition, triglycerides and LDL cholesterol were lowered, and HDL cholesterol was increased, suggesting beneficial metabolic effects as well.[43] Studies in patients with type 2 diabetes without fatty liver disease have not been reported so far.

Glucagon receptor antagonists

Given the important role of (usually elevated) glucagon concentrations in the causation and maintenance of hyperglycaemia.[44,45] However, employing glucagon receptor agonists is a rational approach to treating type 2 diabetes. Clinical studies with glucagon receptor antagonists have been reported over the past 20 years.[22–25,46–48] Compounds like LY2409021,[22,25,48] PF-06291874,[23,49] RN909,[50] RVT-1502,[24] and LGD-6972[51] lower plasma glucose and HbA_{1c}. Typical adverse events commonly reported are elevations in serum liver transaminases[22,23,25,47,49] and increased hepatic triglycerides,[25] indicating some hepatotoxicity, and elevated blood pressure,[25] as well as elevations in LDL cholesterol.[23,49] In addition, glucagon receptor antagonism can upregulate proglucagon expression in intestinal L cells, with subsequent elevations in plasma GLP-1.[52] Some of these effects are reminiscent of the phenotype of rodents deficient in glucagon receptors[53,54] (α cell hyperplasia and hyperglucagonaemia). Given the leading role of glucagon in the defence against hypoglycaemia, theoretically glucagon receptor antagonists might interfere with recovery from hypoglycaemic episodes in patients receiving treatment with insulin or insulin secretagogues. In addition, withdrawing a glucagon receptor antagonist intentionally or inadvertedly might provoke rebound hyperglycaemia. However, hypoglycaemic episodes have not been a prominent problem in the clinical trials with glucagon receptor antagonists (table 1). It is also noteworthy that at the same time activating the glucagon receptor is being studied as an alternative treatment concept for obesity and type 2 diabetes.

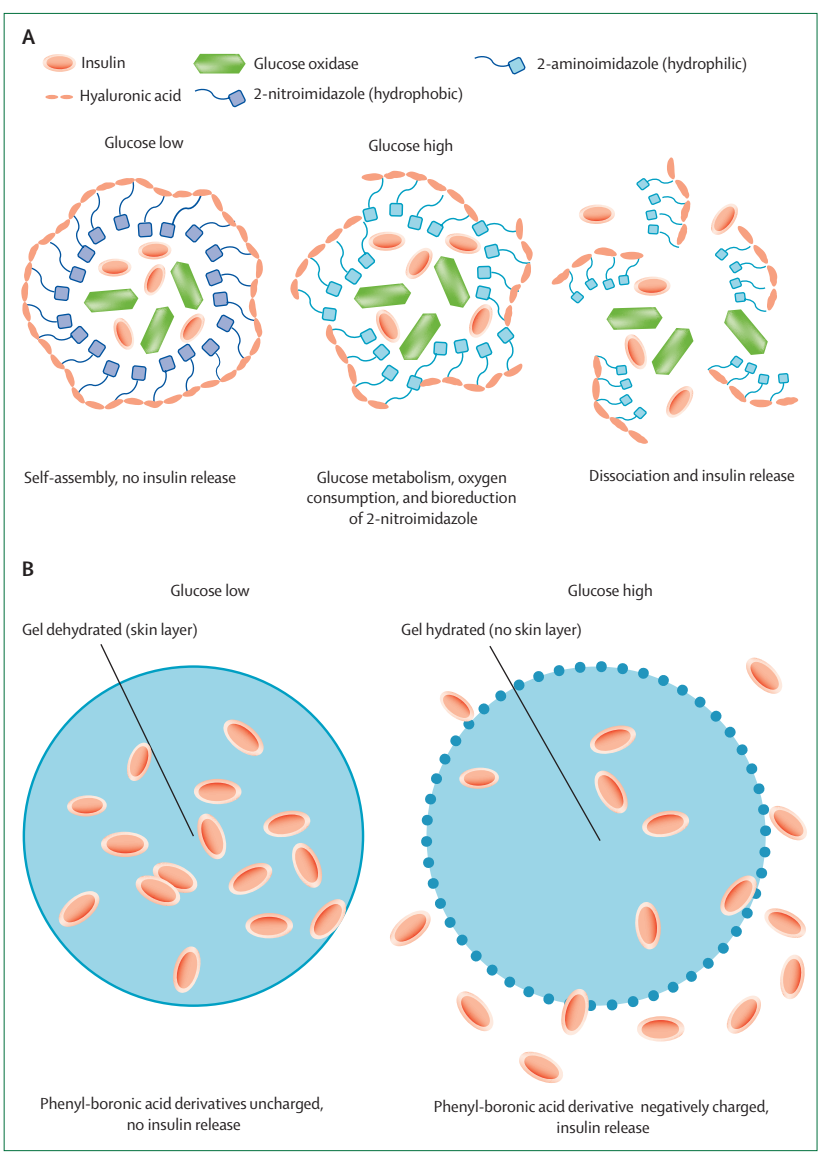

Figure 1: **Potential mechanisms suitable for glucose-dependent insulin release**
Schematic diagram illustrating potential mechanisms suitable for glucose-dependent insulin release from glucose-responsive vesicles (A), which dissociate in the presence of high glucose concentrations due to the consequences of hypoxia generated by the metabolism of glucose by the enzyme glucose oxidase,[53] and (B) from so-called smart gels losing their skin layer due to complex formation of phenylboronic acid with glucose (negatively charged) leading to hydration and dissolution of a skin layer around nanogels preventing insulin release.[54]

	Approximate glycaemic efficacy (HbA_{1c})	Effects on bodyweight	Known effects on cardiovascular events	Putative advantages related to this mechanism	Typical adverse events and problems related to this mechanism	Comment
PPAR agonists: PPARα, PPARγ (glitazones), PPARΔ , and promiscuous (glitazars)	–0·8%*	Approximately 2 kg increase (subcutaneous adipose tissue and fluid retention)	Some evidence for reduced risk from cardiovascular outcomes trials; primary endpoint of ProACTIVE (pioglitazone) not significant;[17] IRIS trial shows benefits regarding recurrent cerebral ischaemia[18]	Only pharmacological approach to directly address insulin resistance; multiple effects suggesting anti-atherosclerotic actions[19]	Fluid retention; congestive heart failure; bone fractures[17,20]	Current reviews still recommend use in type 2 diabetes, however, at lower doses than originally studied, and with great care to avoid adverse events;[20] pharmacologically, novel agents are still being developed[20,21]
Glucagon receptor antagonists	–0·8%*	Increase	No cardiovascular outcomes trials available	Opposes the role of (elevated) glucagon on hepatic glucose production (interference with a pathophysiologically important mechanism)	Increased systolic blood pressure;[22,23,24] increased liver transaminases;[23,25] increased liver fat;[25] increased lipids,[25] not uniformly observed;[24] impaired hypoglycaemia counter-regulation	Some major pharmaceutical companies have terminated their development programmes
Glucokinase activators	–0·8%*	Increase	No cardiovascular outcomes trials available	Activates an enzyme with a central role in β cell and liver cell glucose uptake (making β cells and hepatocytes work as if there was a higher degree of hyperglycaemia)[26]	Increased systolic blood pressure;[27] increased triglycerides;[27,28] increased risk for hypoglycaemia,[27-30] not in all studies;[31] lack of durability (even within a few months)[27,28]	Some major pharmaceuticals have terminated their development programmes; hepato-selective agents might have better effectiveness and safety [32]
11 β-hydroxysteroid dehydrogenase inhibitors	Modest reductions (–0·3 to –0·6%) [33,34]	Decrease[34]	No cardiovascular outcomes trials available	Reduces intracellular cortisol concentrations in tissues equipped with 11 β-hydroxysteroid dehydrogenase[35]	Limited effectiveness; mainly effective in patients with obesity (BMI>30 kg/m²)	Moderate improvements in blood pressure[34] and bodyweight;[33,34] increased LDL cholesterol[34]

PPAR=peroxisome proliferator-activated receptor. *Approximate mean value based on published clinical study results.

Table 1: **Pharmacological mechanisms to treat type 2 diabetes that have been extensively studied, but can no longer be called promising because of a negative risk-benefit relationship**

Glucokinase activators

Glucokinase is the enzyme phosphorylating glucose upon entry into liver and pancreatic β cells. Activating this process means that intracellular glucose 6-phosphate concentrations (phosphorylated glucose) increase, so that more glucose 6-phosphate is available for triggering insulin secretion or for hepatic glycogen synthesis or glycolysis, than would be available at the same circulating plasma glucose concentrations in the absence of glucokinase activation. Both processes contribute to a reduction in glycaemia. The rationale of glucokinase activation and details of the mechanisms have been excellently reviewed.[26,55]

Clinical trials with glucokinase activators have shown effects on HbA_{1c} similar to the DPP-4 inhibitor sitagliptin, but less compared to the sulfonylurea glimepiride (PF-04937319),[31] whereas the glucokinase activator AZD1656 was similarly effective as glimepiride.[56] Variable effects have been reported regarding fasting plasma glucose, ranging from relatively small reductions (MK-0941,[27] HMS5552,[29] AZD1656 compared with glimepiride[56]) to reductions reflecting overall effects on HbA_{1c}.[28–30,57] A typical response seems to be a low after breakfast plasma glucose concentration approaching the hypoglycaemic range, especially with higher doses.[29] Substantial differences exist in the rate of reported hypoglycaemic episodes, ranging from occasionally only[28,31] to 9–23% of patients affected,[29,56] more frequent than with sitagliptin treatment,[58] but less frequent than with glipizide[56] or glimepiride[31] treatment. MK-0941 treatment, dose-dependently, increased the proportion of patients reporting hypoglycaemic episodes to more than 50%.[27] Glucokinase activators AZD6370 and AZD1656 do not effectively interfere with hypoglycaemic counter-regulation in healthy patients.[59] Exogenous glucagon is efficient in eliciting a recovery from insulin-induced hypoglycaemia in AZD1656-treated patients.[60] Clinical studies with a duration of less than 12 weeks observed initial reductions in HbA_{1c} that were not maintained for 4–6 months,[27,28] indicating a durability problem (table 1). Since the durability problem is shared with another class of insulinotropic glucose-lowering medications, the sulfonylureas, it might be related to β-cell stress induced by enhancing rates of insulin production and secretion.

Several glucokinase activator trials have reported significant elevations in triglycerides, LDL cholesterol, and non-HDL cholesterol as well as reductions in HDL cholesterol,[27,28,30] whereas other studies only reported changes in triglycerides[56] or no changes.[31] Increased blood pressure has been described in some studies,[56,27] but not in others.[31] Increased serum activities of liver

transaminases, usually within the normal range, have been reported.[28,30] As a rule, bodyweight did not change with glucokinase activator treatment.

Although the glucose-lowering profile of glucokinase activators described so far cannot uniformly be called attractive or competitive in comparison with other mechanisms or approaches, the description of TTP399 by Vella and colleagues,[32] suggests a possible viable direction for future clinical use. In their 6-month study with TTP399 (a hepato-selective glucokinase activator), Vella and colleagues reported a HbA_{1c} reduction of 0·9 %, a putatively beneficial rise in HDL cholesterol, a reduction in bodyweight (amounting to 3·4 kg in those with a baseline value of more than 100 kg), and no detrimental effect on lipoprotein patterns or liver enzymes. Also, there was no rise in blood pressure and a prevalence of hypoglycaemic episodes just slightly higher than with sitagliptin.[32] TTP399 is taken up into hepatocytes, but much less so into pancreatic β cells.[32]

Inhibitors of 11ß-hydroxysteroid dehydrogenase (11ß-HSDH)

The 11β-HSDH enzyme is responsible for regenerating the bioactive glucocorticoid cortisol intracellularly from the relatively inactive cortisone, mainly in the liver and adipose tissue.[35] In patients with obesity and normal glucose tolerance, 11β-HSDH activity is elevated in adipose cells, but reduced in the liver; in patients with obesity and type 2 diabetes, 11β-HSDH activity is also elevated in adipose cells, but not increased in the liver.[61] Rodents overexpressing 11β-HSDH in adipose tissue develop insulin resistance and features of the metabolic syndrome,[62] thus providing a rationale for therapeutic 11β-HSDH inhibition. Clinical trials with 11β-HSDH inhibitors (INCB13739,[33] MK-0916,[34] and UE2343)[34] indicate effective enzyme inhibition in vivo, but only minor reductions in HbA_{1c} (ranging from 0·3[34] to 0·6%),[33] minor bodyweight reduction (approximately 1 kg),[33,34] and improvements in lipoprotein profiles, in particular in patients with elevated lipids at baseline[33,34] as well as reductions in blood pressure by up to 8 mmHg[34] (not confirmed by Rosenstock and colleagues[33]). 11β-HSDH like RO5093151 might, nevertheless be a valuable medication for reducing hepatic triglycerides in patients with metabolic-dysfunction-associated fatty liver disease.[63]

Uniformly, small, but significant elevations (within the normal range) are reported for adrenocorticotropic hormone[33,64] and adrenal androgens like dehydroepiandrosterone[34] or dehydroepiandrosterone sulfate[33,64] and 4-androstenedione.[64] Even though in recent years new chemical compounds inhibiting 11β-HSDH type 1 have been characterised (details not described here), taken together, the efficacy of this class does not seem to predict a successful further development of 11β-HSDH inhibitors for the treatment of type 2 diabetes.

Promising therapeutic approaches for type 2 diabetes

While in the previous sections, we have summarised developments with limited or questionable effectiveness or benefit–risk relationship, the following sections describe mechanisms without such obvious limitations.

Adiponectin

Adiponectin is a secretory product of adipocytes of white adipose tissue, which, unlike other adipokines, is produced and secreted at higher rates in the presence of a low white (in particular, visceral) adipose tissue mass.[65] It is a polypeptide with 247 amino acids composed of a globular component and a collagenous tail, which physiologically associates into trimers, hexamers, or high-molecular weight complexes of 18–36 molecules.[66–68] Physiologically, it improves insulin sensitivity in liver and muscle by activating AMP kinase, thus reducing hepatic glucose output, de novo lipogenesis, and triglyceride storage (figure 2).[66–68] Adiponectin directs triglyceride storage towards subcutaneous adipose tissue, reduces lipid overload and associated lipotoxicity and dysfunction in muscle, liver, and the pancreas.[66–68] In addition, it exerts anti-inflammatory and antifibrotic actions and reduces oxidative stress.[66–68] Overall, the spectrum of biological activities of adiponectin suggests beneficial effects regarding glycaemic control, but also concerning lipoprotein metabolism,[69] cardiovascular consequences,[68] and fatty liver disease.[70] Based on these biological features, a therapeutic potential has been explored for adiponectin or its derivatives. Thiazolidinediones (PPARγ agonists) exert most of their therapeutic effects on insulin sensitivity through augmenting the secretion of adiponectin from adipocytes,[71] such that therapeutic effects are not observed in animals with a deletion in the adiponectin gene or in its receptors.[72] Some other approaches of making therapeutic use of adiponectin are listed and described in the appendix (p 7). The ideas range from using transfection with adiponectin cDNA to administrations of recombinant adiponectin and small-molecule mimetics of adiponectin. Furthermore, imidazoline compounds might be secretagogues for adiponectin,[73] and peptides modulating assembly of the adiponectin polypeptide in the endoplasmic reticulum might facilitate its appearance in the circulation.[74] Angiotensin receptor antagonists or angiotensin-converting enzyme inhibitors,[75] garlic extract, the phytochemicals astragaloside II and isoastragaloside I, cobalt, and manganese might stimulate adiponectin secretion as well.[76] Macrophage-specific promotors have been developed to enhance adiponectin availability in blood vessels to interfere with lipid accumulation and atherogenesis.[77]

The effects of various approaches leading to enhanced stimulation of adiponectin receptors vary with respect to the degree of glucose-lowering observed (appendix p 7). To our knowledge, none of the approaches summarised in the appendix (p 7) has been carried forward into

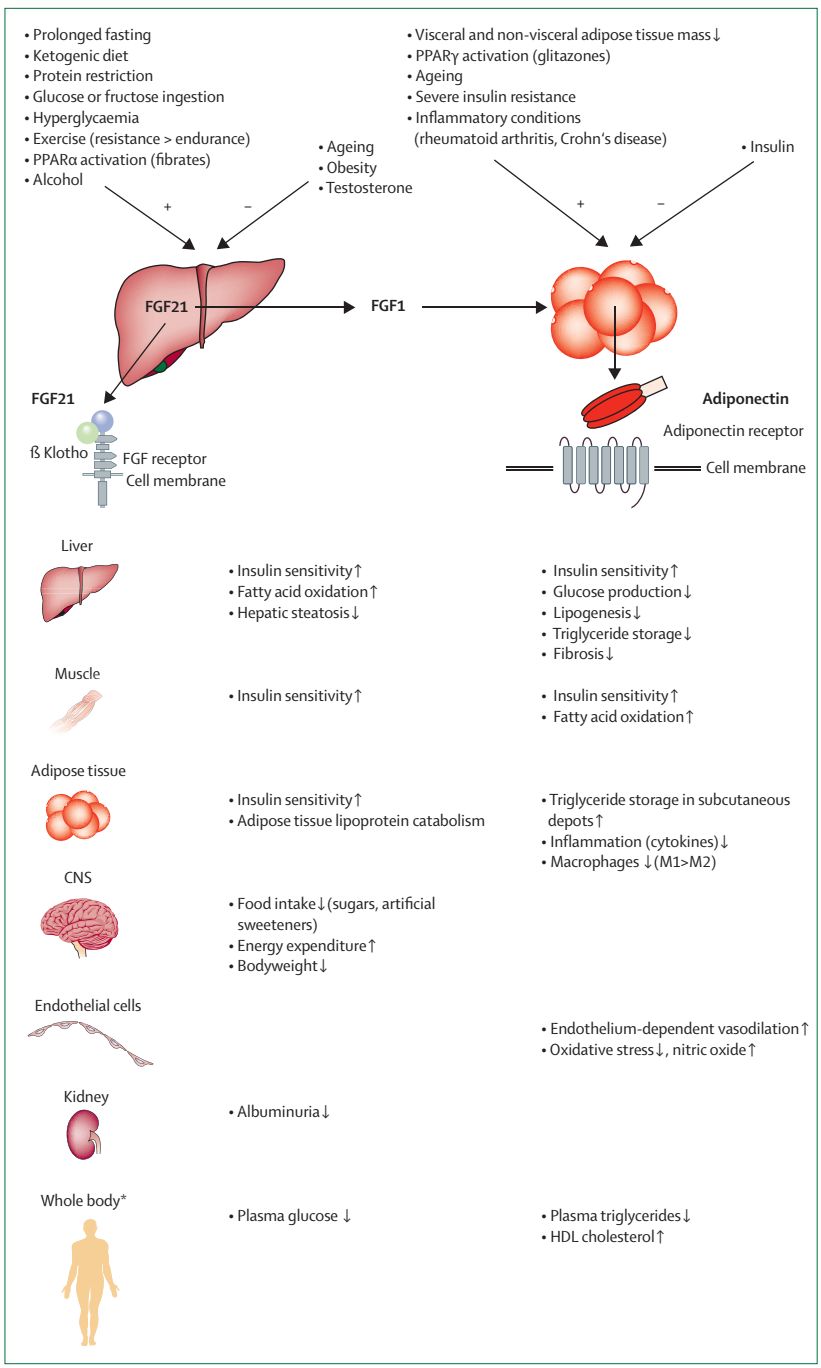

***Figure 2*: Production and secretion of FGF21 and adiponectin and their biological effects on the body**
Secretion of FGF21 (mainly from the liver) and of adiponectin (mainly from adipose tissue) under the influence of biological and chemical stimuli and biological effects elicited in various tissues and cell types. FGF21 potently stimulates adiponectin release, so that the biology of FGF21 and adiponectin are tightly interconnected. ↑increased. ↓decreased. >greater effect (ie, resistance training has greater effect than endurance training on FGF21 secretion; M1 macrophages are more suppressed compared with M2 macrophages).*Multiple organs and tissues are involved in these biological effects

studies involving human participants. One reason for this might be the recent concern from epidemiological studies that high concentrations of circulating adiponectin appear to be associated with worse cardiovascular outcomes, in particular, a higher mortality.[68,78,79] So far, we have no mechanistic explanation for these surprising findings that seem to contradict the known profile of biological actions of adiponectin. Also, it is not known whether this risk applies to the therapeutic use of adiponectin-based strategies as well.

FGF21

FGF21 is mainly produced in the liver and secreted into the circulation due to an absence in the canonical heparan-binding domain, which is characteristic for other, non-endocrine FGFs.[80] It signals through interaction with FGF receptor 1c and a co-receptor protein, β-klotho.[80] Some factors determining the secretion of FGF21 from the liver are summarised in figure 2. Adiponectin secretion is prominently stimulated by FGF21[81] and by FGF21 derivatives (table 2). Established biological effects include a reduction in bodyweight, mediated by reduced food intake and increased energy expenditure. In animals, increased energy expenditure can involve sympathetic activation of brown adipose tissue thermogenesis.[80] FGF21 increases insulin sensitivity and, under certain circumstances, reduces plasma glucose in diabetic animal models. This reduction in glucose depends on adiponectin release and the stimulation of adiponectin receptors,[81] whereas effects on bodyweight do not.[81] In addition, lipid metabolism is affected by FGF21: typically, triglycerides are reduced, HDL cholesterol is increased, and small, dense LDL particles are reduced by FGF21[94] by accelerating lipoprotein metabolism in adipose tissue (figure 2).[95] Hepatic steatosis could be reversed by FGF21.[96]

Table 2 compiles recent attempts to substantiate a therapeutic potential for FGF21-based approaches in preclinical and clinical studies. FGF21 derivatives have been developed by modifying the amino acid sequence to increase stability of the molecule, and by fusing it with larger polypeptides (fragments of immunoglobulins) or polyethylene glycol (PEGylation). Although experiments in rodents have usually found robust effects on bodyweight and glycaemic parameters, this was not the case in human phase 1 or 2 clinical trials to the same extent (table 2), pointing to some important species differences in the therapeutic potential of FGF21. Rather, effects on lipid profiles in these human studies yielded robust effects, qualitatively and quantitatively similar to those described in experimental animals (table 2).

The association of high FGF21 plasma concentrations with low target organ FGF receptor 1c and 2c, low β-klotho, and low activity of post-receptor signalling pathways has been termed FGF21 resistance[97] and has raised concern as to whether this might impair therapeutic effects of exogenous FGF21 or its analogues. However, in mouse models of obesity and insulin resistance, exogenous FGF21 still caused reductions in plasma glucose and bodyweight,[98] thus challenging a key effect of FGF21 resistance. Human data on potential

	Structure	Pharmaco-kinetic details	Therapeutic effects in animal models of diabetes	Therapeutic effects in patients with type 2 diabetes		Comments
				Metabolic parameters	Bodyweight	
LY2405319	FGF21 with additional disulfide bond (L118C-A134C), deletion of N-terminal His-Pro-Ile-Pro, S167A mutation to eliminate O-glycosylation site in yeast	Dose-proportional increments in plasma concentrations with once-daily subcutaneous injections	Streptozotocin-diabetic mice: significantly reduced plasma glucose and increased energy expenditure; diabetic rhesus monkeys: significantly reduced triglycerides, increased HDL cholesterol, not significantly changed or reduced LDL-cholesterol, reduced VLDL cholesterol, and increased adiponectin	Insignificant trend towards plasma glucose reduction; significantly reduced triglyceride; reduced LDL-cholesterol	Reduction (range 1·2 kg)	Marked differences between animal and human studies[82–84]
PF-05231023	[Des-His1, Ala129Cys] FGF21/human IgG1κ conjugate	Elimination half-life approximately 7 h	*ob*/*ob* mice: reduced plasma glucose and reduced bodyweight; cynomolgus macaques: reduced food intake and reduced bodyweight	Insignificant trend: plasma glucose reduced; significantly reduced triglycerides; increased HDL cholesterol; not significantly changed or reduced LDL-cholesterol; increased adiponectin	Reduction (approximately 5 kg)	Marked differences between animal and human studies[85–87]
BMS-986036 (pegbelfermin)	PEGylated recombinant FGF21, exchanged unique amino acid p-acetyl phenylalanine serves as PEGylation site for oxime bond formation	Suitable for once-weekly dosing	Streptozotocin-induced diabetic mice: reduced plasma glucose (HbA_{1c}); increased glucokinase and GLUT-1 (liver, glucose uptake and glycolysis); reduced PEPCK or glucose-6 phosphatase (liver, gluconeogenesis)	No change in plasma glucose or HbA_{1c}; increased adiponectin	No significant change	Marked differences between animal[88,89] and human studies[90,91]
AKR-001 (AMG 876)	Human immunoglobulin G1 Fc fusion protein (amino acid substitutions P171G, A180E)	Elimination half-life 2·5–3·5 days	Reduced bodyweight; reduced plasma glucose; significantly reduced triglycerides; increased HDL cholesterol	Reduced plasma glucose; significantly reduced triglycerides; increased HDL cholesterol; reduced non-HDL cholesterol	Non-significant trend (reduction)	Similar results in animal[92] and human[93] studies, except for bodyweight

FGF21=fibroblast growth factor 21. VLDL=very low-density lipoprotein. PEPCK=phosphoenolpyruvate carboxykinase. GLUT-1=glucose transporter-1.

Table 2: **Fibroblast growth factor 21-based compounds for the therapy of type 2 diabetes, obesity, and fatty liver disease in animal and human studies**

FGF21 resistance are not available to the best of our knowledge.

LY2405319 is a modified FGF21 with a few amino acid exchanges (to stabilise the polypeptide and to allow large-scale synthesis in yeast).[99] LY2405319, in insulin-deficient mice, elicits major reductions in plasma glucose, in part mediated through brown adipose tissue.[82] In diabetic rhesus monkeys, LY2405319 caused major reductions in plasma glucose and improvements in the lipid profile, while adiponectin plasma concentrations were stimulated 4 fold.[83] In patients with obesity and type 2 diabetes, however, daily injections of LY2405319 for 4 weeks, corrected dyslipidaemia and led to minor weight reduction, but only showed a non-significant trend towards reduced plasma glucose concentrations.[84] These results might point to important species differences in the pharmacological profile of FGF21 (table 2).

PF-05231023, a [Des-His1, A129C]FGF21/human IgG1κ conjugate, reduces plasma glucose after an oral glucose load in *ob*/*ob* mice, and causes bodyweight reduction in diet-induced obese mice.[85] In non-human primates, it reduces food intake and bodyweight by approximately up to 15% of baseline bodyweight and substantially lowers triglycerides.[86] In human patients with type 2 diabetes, twice weekly subcutaneous injections of PF-05231023 over 4 weeks reduced bodyweight by up to 5–6 kg, plasma triglyceride concentrations by up to 50%, LDL cholesterol by up to 25%, and raised HDL cholesterol by up to 25%,[86,87] however, without major effects on plasma glucose.[86,87] Although the small effects on glycaemia might be disappointing, bodyweight reduction and improvements of lipoprotein profiles might still be of therapeutic value (eg, for improving non-alcoholic fatty liver disease [NAFLD]).

BMS-986036 (pegbelfermin) is a PEGylated recombinant human FGF21.[90] High doses achieved by once-daily or once-weekly subcutaneous administration reduced LDL cholesterol and triglycerides and raised HDL cholesterol.[90] Transaminases were reduced and there were no major changes in plasma glucose and HbA_{1c}.[90] Consequently, pegbelfermin has been studied specifically in patients with NAFLD, showing similar changes in lipoprotein profiles, and a reduction in intrahepatic triglyceride and markers of fibrosis.[91] Other studies have used PEGylated FGF21 in insulin-deficient diabetic mice and found substantial reductions in plasma glucose combined with improvements in lipid profiles in mouse models of type 1[88,100] and type 2 diabetes (table 2).[89,101]

AKR-001 is an FGF21 analogue suitable for once-weekly or bi-weekly subcutaneous injection.[93] In patients with type 2 diabetes, treatment with AKR-001 for 1 month dose-dependently reduced plasma glucose, non-HDL cholesterol, and triglycerides significantly, with reductions in insulin and C-peptide indicative of improved insulin sensitivity.[93] Bodyweight only showed a minor trend towards reduction (table 2).[93]

Other compounds like Fc-FGF21 (RG)[92] or FGF21[SS] (aiming at dynamic folding modulation)[102] have shown similar efficacy in preclinical studies.

Collectively, clinical data summarised in table 2 argue in favour of a therapeutic potential of FGF21 analogues in human type 2 diabetes with consistent results regarding substantial improvements in lipid profiles and hepatic lipid handling. However, in contrast to studies in various animal models there is less effectiveness with respect to lowering plasma glucose and variable results concerning body weight reduction.

FGF1

Animals deficient in FGF1 develop insulin resistance and diabetes characterised by rapid worsening and progression.[103] Physiologically, FGF1 is prevented from circulating by binding to heparan sulfate proteoglycans, thereby only allowing local, paracrine effects.[104] However, when this endothelial barrier is circumvented by subcutaneous or intraperitoneal injection, FGF1 can act as an endocrinised factor to lower plasma glucose in rodent models of type 2 diabetes.[104,105] Some characteristics of the glucose-lowering effects of peripheral FGF1 administrations in diabetic rodents are listed in the appendix (p 8). Even more impressive, minute amounts of FGF1 administered intracerebroventricularly or directly into the hypothalamic arcuate nucleus or median eminence result in dramatic reductions in plasma glucose (into the normal range) that lasts for several weeks or even months.[104,106,107] The main mechanism explaining the reduction in plasma glucose is an increased glucose clearance from the circulation, most likely triggered by an enhanced glucose uptake into the liver (increased activity of glucokinase).[106] The deterioration of β-cell function and mass, which is typical for some animal models of type 2 diabetes (and for human type 2 diabetes) can be delayed by administration of FGF1 into the CNS or peripherally.[108] Studies in rodents suggest that β-cell differentiation could be improved.[109] An interference with the hypothalamic–pituitary–adrenal axis has also been claimed to be a major mechanism.[110] Open questions delaying the translation into human studies are mitogenic functions of FGF1,[104] which can be mitigated by interfering with FGF1-FGF receptor dimerisation,[111] or by deleting the N-terminal 24 amino acid residues.[105] Since administering FGF1 into the cerebrospinal fluid would be of interest, intranasal administrations of FGF1 with added absorption enhancers has been successfully tested in animals.[112,113]

	Changes typical for type 2 diabetes	Pharmacological actions of imeglimin	
		Early (≤2 weeks)[114]	Long-term (>2 weeks)[115]
Pancreatic β cells	Decreased glucose-dependent insulin secretion; increased apoptosis; decreased β-cell mass; increased oxidative stress	Increased glucose-dependent insulin secretion (non-significantly changed amino acid-induced insulin secretion)	Increased glucose-dependent insulin secretion (non-significantly changed amino acid-induced insulin secretion); decreased apoptosis; increased β-cell mass; decreased oxidative stress
Panreatic α cells	Increased glucagon secretion	Non-significantly changed glucagon secretion	Not reported
Hepatocytes	Decreased hepatic insulin sensitivity; decreased fatty acid oxidation; increased liver fat; decreased mitochondrial function; increased reactive oxygen species production; decreased respiratory chain complex III activity; increased hepatic glucose production	Non-significantly changed liver fat; non-significantly changed hepatic insulin sensitivity; non-significantly changed hepatic glucose production	Increased hepatic insulin sensitivity; increased fatty acid oxidation; decreased liver fat; increased mitochondrial density; decreased reactive oxygen species production; increased respiratory chain complex III activity
Myocytes	Decreased muscle insulin sensitivity	Non-significantly changed muscle (whole body) insulin sensitivity	Increased muscle insulin sensitivity (protein kinase B phosphorylation); non-significantly changed whole body insulin sensitivity (homeostatic model assessment)
Endothelial cells[116]	Increased reactive oxygen species production	Non-significantly changed mitochondrial respiration (oxygen consumption and lactate production); decreased reactive oxygen species production; closure of mitochondrial permeability transition pore	Not reported
Whole body	Increased plasma glucose or HbA_{1c}; increased bodyweight and BMI; increased blood pressure; increased lipid disorders	Not studied	Decreased HbA_{1c}; non-significantly changed or slightly decreased bodyweight and BMI; non-significantly changed blood pressure; non-significantly changed triglycerides

Table 3: **Imeglimin mode of action**

Imeglimin

The tetrahydrotriazene compound imeglimin is synthesised from metformin and might be the first example of glimins, a novel class of glucose-lowering medications. Imeglimin seems to have multiple mechanisms of action, which will affect plasma glucose concentrations by improving insulin secretion from β cells of the endocrine pancreas,[114,117,118] enhancing insulin sensitivity (primarily in skeletal muscle),[118] preventing insulin resistance induced by high-fat feeding,[115] and by suppressing hepatic gluconeogenesis[118] (through reducing the expression of gluconeogenic enzymes like glucose 6-phosphatase and phosphoenolpyruvate carboxykinase). Imeglimin induces hepatic lipid oxidation and reduces triglyceride deposition in the liver,[115] indicating some potential for beneficial effects in patients with fatty liver disease. In the endocrine pancreas, β cells are protected from apoptosis induced by cytokines,[118] and an increased β cell-mass could be the result of imeglimin treatment under certain circumstances.[115] Imeglimin seems to improve mitochondrial function in the liver[115] as well as in β cells and reduces mitochondrial-derived free radicals,[115] counteracts the hyperglycaemia-induced oxidative stress, and

might reduce damage associated with reactive oxygen species.[119] Imeglimin prevented endothelial cell death[116] and improved left-ventricular function, acetyl choline-mediated coronary relaxation and flow-mediated mesenteric artery dilatation in *fa/fa* (Zucker) rats.[120] It also reduced mitochondrial reactive oxygen species generation form left ventricles and renal albuminuria and fibrosis (table 3).[120]

The stimulation of insulin secretion in response to hyperglycaemia has been confirmed in people with type 2 diabetes.[121] 12-week trials have described a reduction in HbA_{1c} (*vs* placebo-treated patients) by 0·4% in metformin-treated patients with type 2 diabetes,[122] and 0·7% in sitagliptin-treated patients.[123] 24 weeks of treatment in Japanese patients reduced HbA_{1c} by up to 1·0%. The incidence of hypoglycaemic episodes was not enhanced, and there were no changes in bodyweight.[122–124]

Imeglimin improves glycaemic control but reduces HbA_{1c} only moderately. What sparks interest in potential future use in patients with type 2 diabetes are the multiple mechanisms of action and the improvement of mitochondrial function observed in preclinical studies (table 4). This improvement could address a core defect of type 2 diabetes and prevent the progression in severity that typically characterises long-term trajectories of glycaemic control observed with conventional therapeutic approaches.

Other approaches of influencing mitochondrial function (eg, using a controlled-release mitochondrial protonophore) beneficially reduce hepatic triglycerides in high-fat-fed rats with steatohepatitis and diabetes, but also reduce fasting glucose as well as glycaemic and insulin excursions (suggesting improvements in insulin resistance) after an intraperitoneal glucose load.[125] The same controlled-release mitochondrial protonophore was effective in a model of NAFLD related to genetic microsomal triglyceride transfer protein deficiency.[126]

Agonists for G-protein-coupled receptors

G-protein-coupled receptors GPR40, GPR119, and GPR120 are expressed in pancreatic β cells and appear to be involved in the stimulation of insulin secretion by their primary ligands, medium and long-chain fatty acids. GPR40, GPR119, and GPR120 are also expressed in enteroendocrine L cells and their stimulation with non-esterified fatty acids,[127] 2-oleoyl glycerol,[128] oleoylethanolamide,[129] or orally absorbable specific agonists[130] results in augmented release of GLP-1 and GIP. The GPR40 agonist TAK-875 (fasiglifam) has been tested in clinical trials and was found to reduce HbA_{1c} by up to 1·4%, accompanied by negligible weight gain, and with a low incidence of hypoglycaemia (table 4).[131–134] The development was stopped due to hepatotoxicity observed in the overall clinical programme,[135] which might be related to the generation of reactive oxygen species[136] or to an inhibition of hepatobilary transporters.[137] It is unknown, whether this might be a class effect. Furthermore, GRP40 agonists (Yhhu4488)[161] and GPR119 agonists (DS-8500a,[162] GSK1292263)[163] are being developed, and a clinical trial with DS-8500a has been reported, which not only describes reductions in HbA_{1c} but also improvements in lipoprotein profiles.[162] HBK001 is a molecule that has a dual role as GPR119 agonist and as a DPP-4 inhibitor and stimulates insulin secretion in metabolically healthy and diabetic mice.[164,165]

GLP-1 secretagogues

Since doubling nutrient-related GLP-1 responses with DPP-4 inhibitors are sufficient to elicit meaningful reductions in plasma glucose and HbA_{1c}, stimulating GLP-1 release from intestinal L cells might be of interest. Ingestion of L-arginine[138] or glutamine[139] raises GLP-1 (and peptide YY)[138] plasma concentrations (table 4). However, the effect size might be too small to raise expectations that this might translate into significant improvements in glycaemic control.[166]

Bile acids stimulate GLP-1 secretion by interacting with TGR5 (also called GPBAR1), a bile acid receptor expressed in L cells.[167] Other compounds interacting with TGR5 have also been described to augment GLP-1 release from L cells: compounds isolated from a plant, *Fagonia cretica*, which is postulated to have glucose-

	Mechanism of action	Glucose-lowering activity	Other aspects to be considered	Stage of development
Controlled-release mitochondrial protonophore	Mitochondrial uncoupling agent (liver specific)[125,126]	Robust	Reduction in hepatic triglyceride content	Pre-clinical
G-protein-coupled receptor ligands (GPR40, GPR119, and GPR120)	Increased incretin hormone secretion; increased insulin secretion[127-137]	Robust	Hepatic adverse events	Phase 2
L cell (GLP-1) secretagogues	Accentuated release of endogenous GLP-1 to reach pharmacological effectiveness[138-143]	Potentially high	Synergistic effects with DPP-4 inhibitors	Proof-of-principle studies (animals and humans)
Small molecule (orally absorbed) GLP-1 receptor agonists	GLP-1 receptor agonism (increased insulin secretion, reduced glucagon secretion, reduced bodyweight)[144-147]	Potentially high	Strategies needed to avoid nausea and vomiting as adverse events	Phase 1
N-methyl-D-aspartate receptor agonists (eg, dextromethorphan)	Increased insulin secretion, increased ß-cell survival[148-150]	Robust	Possible interference with diabetes progression	Phase 2
Ranolazine (anti-anginal agent)	Unknown (discovered by serendipity)[151-156]	Robust	Cardiovascular benefits (improvement in flow-mediated vasodilation)	Phase 3
Imatinib (tyrosine kinase inhibitor approved as antineoplastic agent)	Improvements in ß-cell health and function[157-160]	Case report: remission of type 2 diabetes	To be explored	Case report, pre-clinical studies

GLP-1=glucagon-like peptide-1. DPP-4=dipeptidyl peptidase-4.

Table 4: **Overview of novel classes of glucose-lowering medications, their mechanisms of action, and their effect on plasma glucose or HbA_{1c} and other risk factors**

lowering potency,[140] 3-(1-methylethyl)-9b.phenyl-[1,3] oxazolo[2,3-a]isoindole-2,5(3H.9bH)-dione,[141] and RO5527239.[142] Tetrahydrobenzimidazole TGR5 agonists potently increase GLP-1[143] and these and similar agents improved glucose tolerance in mice (table 4).[143,168]

GLP-1 receptor stimulation

Peptide-based GLP-1 receptor agonists have acclaimed a prominent role in the treatment of type 2 diabetes, as effective regarding glycaemic control as (basal) insulin, with the added benefits of not provoking hypoglycaemic episodes, reducing bodyweight, and preventing clinical cardiovascular events like myocardial infarction, stroke, and cardiovascular death.[169] Furthermore, the LEADER,[170] SUSTAIN-6,[171] and REWIND[172] studies have shown a prevention of clinically important renal composite endpoints (new onset of persistent macroalbuminuria, persistent doubling of serum creatinine, necessity for renal replacement therapy, and death from renal causes) with subcutaneous once-daily liraglutide,[170] once-weekly semaglutide,[171,173] and dulaglutide[172] injections. The single endpoint most affected was macroalbuminuria. These results might underestimate the reno-protective potential of GLP-1 receptor agonists, since only a limited number of patients with pre-existing chronic renal disease or microalbuminuria were studied, and the duration of follow-up was short, in particular for SUSTAIN-6.[171]

An oral preparation of semaglutide (slightly modified amino acid sequence of GLP-1 with a fatty acid side chain) has been developed, supporting absorption of semaglutide from the gastric mucosa with help of the absorption enhancer sodium N-[8-(2-hydroxybenzoyl)amino] caprylate.[174] This preparation needs to be ingested with limited volumes of water (120 ml) on an empty stomach, and further intake of additional fluid, nutrients, and other medications needs to be deferred by at least 30 min to guarantee reliable absorption. The bioavailability is still low, but sufficient to support clinical effects on plasma glucose and HbA_{1c} as well as bodyweight with comparable effects between once-daily oral intake of semaglutide and subcutaneous administration once a week.[174] A head-to-head comparison with subcutaneous liraglutide, an established GLP-1 receptor agonist often used for benchmarking,[169] showed superiority of semaglutide with respect to lowering HbA_{1c} (small difference after 52 weeks) and bodyweight reduction (more marked difference).[175] A preliminary cardiovascular outcomes trial with relatively small numbers of patients and short follow-up nevertheless showed cardiovascular benefits.[176]

Going even further, small molecules acting as GLP-1 receptor agonists[177–179] or positive allosteric modulators of the GLP-1 receptor[180] have been identified. These molecules raise cAMP concentrations in β cells in a glucose-dependent manner,[177,178,180] stimulate insulin secretion,[177,180] and lower glucose in experimental diabetes animal models.[177,180] It is anticipated that such small molecules would be readily absorbed after oral ingestion. However, detailed pharmacokinetic information on these novel compounds is not available so far.

Based on a better understanding of the interaction of GLP-1 receptors with their ligands, novel compounds that bind with high affinity to the GLP-1 receptor have been developed: RGT1383,[144] LY3502970,[145] TT-OAD2,[146] and PF-06882961 (danuglipron),[147] some of which have shown glucose-lowering activity in non-human primates[145] and in patients with type 2 diabetes (table 4).[147]

On the other side of the spectrum, there have been attempts to provide a steady supply of GLP-1 from subcutaneous depots, to avoid repeated injections at short intervals and problems associated with so-called peak and trough pharmacokinetic profiles, which might be associated with undesirable side effects. Protease operated depots are protease-cleavable oligomers of GLP-1 added to a thermally responsive, depot-forming elastin-like polypeptide, which undergoes a thermally triggered inverse-phase transition below body temperature, making it suitable for forming a subcutaneous depot.[181] A single injection has reduced plasma glucose for periods up to 5 days in mice.[181] Release from such digestible depots might be associated with even less fluctuation in plasma concentrations as compared with subcutaneous injections of GLP-1 receptor agonists with long elimination half-lives, thus avoiding peaks (side effects) or troughs (periods with reduced efficacy).

Dual and triple agonists

Although peptide agonists stimulating GLP-1 receptors have evolved as highly efficacious,[169] well established medications for improving glycaemic control and achieving bodyweight reduction, we are currently seeing the development of agents with the potential for interacting with two or more different enteropancreatic hormone receptors. The expectation is that such compounds will have a substantially better efficacy and might eventually lead to diabetes remission and substantial reductions in fat mass and bodyweight, very much comparable to what is observed after the most effective procedures of bariatric (metabolic) surgery: Roux-en-Y gastric bypass and vertical sleeve gastrectomy.[182] Although originally bariatric surgery was designed with the assumption that the post-surgical anatomy will introduce a restrictive element prohibiting intake of meals exceeding a small size or caloric load, this view had to be changed. Bariatric surgery changes the gut hormonal milieu substantially, mainly because the post-surgical anatomy favours rapid exposure of lower parts of the gastrointestinal tract with nutrients that trigger and augment release of gastrointestinal hormones, which are typically produced in enteroendocrine cells with higher abundance in these lower intestinal segments. This is the reason for a much-augmented rise in post-meal plasma concentrations of both GLP-1 and peptide YY (table 5) from intestinal L cells, which increase in abundance in further distal

	Meal-related secretion		Biological effects of peptide hormones used as components of dual or triple agonists for the treatment of type 2 diabetes and obesity							
	Roux-en-Y gastric bypass	Sleeve gastrectomy	Gluco-regulatory actions				Bodyweight-regulating actions			
			Insulin secretion	Glucagon secretion	Other	Net effect	Appetite	Energy expenditure	Other	Net effect
GLP-1	Excessively increased[183,184]	Increased[185]	Significantly increased [186] (glucose-dependent)*	Decreased[186] (glucose-dependent)*	Gastric empyting slowed†[187]	Decreased FPG; significantly decreased PPG	Significantly decreased‡[188]	Potentially increased[189] (potentially increased BAT thermogenesis)[190,191]	..	Significantly decreased
Glucagon	Increased[191]	Increased [185]	Increased (minor at physiological concentrations)	No effect	Not significantly changed gastric emptying; increased hepatic glucose production	Increased FPG; increased PPG	Not significantly changed (might potentiate GLP-1 action)[193,194]	Increased [189]	..	Decreased
GIP	Increased [183,184,192]	Variably increased	Significantly increased[186] (glucose-dependent)§	Increased [186]	none	Decreased FPG; decreased PPG	Conflicting data¶[195,196]	No obvious effect	..	Increased, not significantly changed, or decreased
Peptide YY	Significantly increased[197]	Increased [185]	Increased [198] with chronic administration	No immediate effects	Preservation or improvement in β-cell mass and function[198-200]	Hypothetically decreased FPG and PPG (no quantitative data available)	Significantly decreased‡[201]	No obvious effect	..	Decreased

GLP-1=glucagon-like peptide-1. GIP=glucose-dependent insulinotropic polypeptide. BAT=brown adipose tissue. FPG=fasting plasma glucose. PPG=postprandial glucose. *Threshold glucose concentration of approximately 3·7 mmol/l (or 66 mg/dL) for both physiological and pharmacological concentrations of GLP-1 or GLP-1 receptor agonists. †Slowed gastric emptying delays glucose absorption and post-meal glycaemic rises (at physiological and pharmacological concentrations of GLP-1 or GLP-1 receptor agonists). ‡Effective after intracerebroventricular and peripheral administration. §Almost totally absent in patients with diabetic glucose tolerance, even at supraphysiological concentrations of GLP-1 or GLP-1 receptor agonists. ¶Reported findings range from resistance to diet-induced obesity in GIP receptor knock-out animals to dramatic reductions in energy intake after exogenous administration of GIP or GIP receptor agonists in rodents.

Table 5: **Potential role of individual entero-pancreatic hormone receptor stimulation in pharmacological effects on glucose homeostasis and bodyweight reduction when using single molecule multiple hormone receptor (dual or triple) co-agonists**

segments of the gut. A second factor is the rapid transit of ingested nutrients from the gastric remnant into the gut, which could explain an accentuated release of GIP after gastric bypass despite the fact that GIP (K) cells are most abundant in the duodenum,[202] which is excluded from the food passage after the surgery. The reason for higher plasma glucagon concentrations after Roux-en-Y gastric bypass is less clear, and can involve intestinal production of so-called pancreatic glucagon.[202] Typical changes in the pattern of enteroendocrine hormone release associated with bariatric surgery are summarised in table 5. Collectively, these changes create a hormonal milieu that explains a massive reduction in appetite and food (energy) intake and an amelioration of glucose control resulting in substantial improvements in parameters indicating glycaemic control often ranging up to diabetes remission. The insight that such a neuroendocrine input rather than the restrictive nature of bariatric surgery is responsible for the consequences regarding glycaemic control and bodyweight reduction[203] is the fundamental rationale for mimicking these effects by developing agents that address the relevant receptors. Some biological effects of the main candidate hormones important for improving glycaemic control and for reduction in bodyweight are compiled in table 5, with a focus on insulin and glucagon secretion as well as appetite and food intake and energy expenditure.

Target receptors with a potential therapeutic role have been selected because of elevated plasma concentrations of the respective ligand hormone after bariatric surgery (gastric bypass or sleeve gastrectomy): GLP-1 increases to up to 10 fold higher concentrations after gastric bypass[183] (ie, into the concentration range typically reached during treatment with GLP-1 receptor agonists). This increase is observed early after surgery and is maintained for years.[183,184] Similarly, peptide YY, produced in the same L cells, follows the same pattern.[197] Regarding GIP, the increments are reported to be smaller[183] and sometimes not significant.[184,192] Glucagon concentrations rise, in particular after eating.[192] Similar changes are elicited by vertical sleeve gastrectomy (table 5).[185]

Effects of enhanced stimulation of enterohormonal receptors range from immediate changes in insulin and glucagon secretion (GLP-1 and GIP)[186] or maintenance of endocrine pancreatic anatomy resulting in functional improvements (peptide YY)[185,200] to a delay in the onset of or deceleration in gastric emptying (GLP-1),[204] or both, and changes in appetite and energy intake (GLP-1,[205] peptide YY,[201] and perhaps GIP)[196] or energy expenditure (glucagon).[189,206] Combinations of GLP-1 and glucagon (administered at low doses) might more effectively reduce food intake,[193] although this view has been challenged.[194] Combinations of GLP-1 and peptide YY[207] or of GLP-1, oxyntomodulin, and peptide YY (administered

subcutaneously) seem to be particularly effective in this respect.[206] The effects of glucagon on energy expenditure (increased) and substrate oxidation (shifted towards carbohydrate oxidation) might be accentuated by co-administration of GLP-1,[189,193] but this has not been confirmed in other studies.[194] GLP-1, oxyntomodulin, and peptide YY, when co-administered in human volunteers, did not change energy expenditure.[206] Effects of GLP-1 on energy expenditure in rodents have in part been attributed to the stimulation of adipose tissue browning and thermogenesis,[190,208] but this effect does not seem to contribute much to lowering bodyweight with GLP-1.[191] Whether this mechanism is relevant to human bodyweight regulation is unknown. These potential mechanisms are summarised in table 5. In estimating the contribution of certain gut peptide hormones to the effects on glycaemia and bodyweight, there are some uncertainties related to the stimulation of insulin secretion by GIP in patients with type 2 diabetes (which with acute administration even of supra-physiological doses of GIP is very much impaired relative to patients with no impairment of their glycaemic control) and the role of GIP receptor stimulation in the regulation of bodyweight. While findings in GIP receptor knock-out animals (resistance to diet-induced obesity)[195] support an obesogenic role, studies published after 2019 have indicated a role for hypothalamic GIP receptors mediating a reduction in energy intake (table 6).[220,221,222]

Dual agonists targeting GLP-1 and glucagon receptors

One rationale for combining agonism at GLP-1 and glucagon receptors is derived from the properties of oxyntomodulin, a natural proglucagon fragment produced in and released from the intestinal L cells. Oxyntomodulin can stimulate GLP-1 and glucagon receptors, and, when administered pharmacologically, reduces glucose concentrations[223] and bodyweight.[224] Glucagon-receptor agonism adds the ability to increase resting energy expenditure.[225] Therefore, a greater bodyweight reduction is expected from GLP-1 and glucagon co-agonists than from GLP-1 receptor stimulation alone. Single molecules targeting various gut hormone receptors are possible because of the sequence homologies highlighted in the appendix (p 8).

Because glucagon receptor stimulation will most likely raise plasma glucose concentrations, which can be compensated for by the effect on GLP-1 receptors, the major strength of this approach will probably be in bodyweight reduction, and potentially associated effects like reductions in hepatic triglyceride concentrations and hepatic inflammatory and fibrotic responses (table 6). In particular, cotadutide seems to have potential for the treatment of NAFLD.[212] Clinical studies (phase 2) have been reported for cotadutide (MEDI0382)[210] and SAR425899.[213] Further studies with a focus on obesity, liver glycogen, and NAFLD have been completed, but not yet reported at the time of writing.

Twincerins

Dual agonists able to stimulate both GLP-1 and GIP receptors act through maximally stimulating the entero–insular axis.[196] Although NNC0090–2746 displayed a pharmacological effectiveness similar to a selective GLP-1 receptor agonist (liraglutide),[215] tirzepatide was substantially more effective in reducing HbA_{1c} and bodyweight compared with dulaglutide (GLP-1 receptor agonist)[226] and even compared with the most effective GLP-1 receptor agonist, semaglutide (for

	Generic name	Pharmaceutical company	Receptors addressed by the compound	Receptor binding	HbA_{1c} reduction in type 2 diabetes	Bodyweight reduction (kg)	Additional effects		Stage of development
							Human studies	Animal studies	
MEDI0382	Cotadutide	Medimmune and AstraZeneca	GLP-1 and glucagon	Higher affinity for GLP-1 receptor than glucagon receptor[209]	−0·9%[210]	−3·8[210]	Reduced gastric emptying;[211] decreased triglycerides[211]	Reduced hepatic fat[212]	Phase 2b/3
SAR425899	..	Sanofi	GLP-1 and glucagon	Higher potency for GLP-1 receptor than glucagon receptor	−0·6%[213]	−5·5[213]	Reduced gastric emptying[214]	Increased insulin secretion[214]	Phase 2
NNC0090–2746	..	NovoNordisk	GLP-1 and GIP	Equivalent affinity for GLP-1 receptor and GIP	−1·0%[215]	−2·9[215]	Similar to liraglutide[215]	..	Stopped after phase 2a
LY3298176	Tirzepatide	Eli Lilly	GLP-1 and GIP	Higher affinity for GIP receptor than GLP-1 receptor[216]	−2·4%[217]	−11·3[217]	Reduced non-alcoholic steatohepatitis parameters[209]; β-cell function, increased insulin sensitivity[218]	Reduced GLP-1 receptor internalisation (*vs* GLP-1 interacting with the GLP-1 receptor)[219]	Phase 3

GLP-1=glucagon-like peptide-1. GIP=glucose-dependent insulinotropic polypeptide.

***Table 6*: Dual agonists stimulating GLP-1 receptors plus glucagon or GIP receptors, for which studies have been reported**

once-weekly subcutaneous injection).[227] For a given level of effectiveness, gastrointestinal adverse events were less pronounced compared with dulaglutide. Slower initial up-titration further reduces such side effects.[217] The better clinical effectiveness of tirzepatide[226] as compared with NNC0090–2746 could be the result of clearly preferential GIP receptor stimulation.[216] Further research is needed to define the optimum degree of bias (ie, the relative affinities to the GLP-1 *vs* the GIP receptor needed for best efficacy). Given that acute studies show an almost complete unresponsiveness to GIP in patients with type 2 diabetes,[186,228] it is not evident how adding GIP receptor agonism to GLP-1 receptor agonism is responsible for increased effectiveness of tirzepatide than that of dulaglutide, a specific GLP-1 receptor agonist.[226] The long-term effects of stimulating GIP receptors might differ from short-term GIP receptor activation. Improvements in glycaemic control, initially elicited by GLP-1 receptor agonism, might reactivate responses to GIP, as shown for intensified insulin treatment.[229] The net effect of exposure to GIP agonists on bodyweight is also unclear. Although rodents deficient in GIP receptors are resistant to diet-induced obesity,[195] other studies did not find effects of long-acting GIP agonists on bodyweight,[216] but body-weight reduction in response to exogenous GIP agonists has also been described.[196] Human studies employing exogenous GIP do not support a reduction in food intake mediated by GIP receptor stimulation.[230] In four phase 3 trials, 15 mg of tirzepatide once-weekly reduced HbA_{1c} by 2·1%, 2·5%, 2·4%, and 2·6% and bodyweight by 9·9 kg, 12·4 kg, 12·9 kg, and 10·9 kg on average.[227,231,232] The unexplained efficacy of tirzepatide is a driver for research to clarify these open questions. Reasons quoted for the superior effectiveness of tirzepatide versus selective GLP-1 receptor agonists are weight-independent effects improving insulin sensitivity,[233] a recently described role of GIP in suppressing appetite and food intake by interacting with hypothalamic GIP receptors,[220,221] interacting with appetite-reducing effects of GLP-1 receptor agonists in a synergistic manner,[234] and peculiarities in β-arrestin recruitment impacting on receptor internalisation and ligand-induced GIP or GLP-1 receptor, or both, desensitisation.[219]

Other dual and triple agonists

Dual agonists addressing GLP-1 and peptide YY receptors are expected to exploit the prominent reduction in food and energy intake induced by either agent alone,[169,201] with some synergistic activity described recently.[235] Dual agonists that display better effectiveness compared with GLP-1 and peptide YY alone are under development.[236] Unimolecular peptides addressing more than two receptors (eg, GLP-1, GIP, and glucagon receptors) have shown promising effectiveness in animal studies.[196] Clinical developments are expected for the near future.

Treatment strategies for type 2 diabetes with promising results at early stages of development

N-methyl-D-aspartate receptors (NMDAR) are expressed on pancreatic β cells.[148] Morphinan-based NMDAR antagonists improve insulin secretion, glucose tolerance and islet survival.[149] Dextromethorphan, a NMDAR antagonist (and over-the-counter antitussive agent) added to the DPP-4 inhibitor sitagliptin increased insulin secretory responses and reduced glycaemic excursions in patients with type 2 diabetes (table 4).[150]

Ranolazine, an anti-anginal agent,[151] was found to reduce HbA_{1c} in clinical trials with cardiological endpoints.[153,154] Studies in patients with type 2 diabetes showed a significant improvement in flow-mediated vasodilation[152] and improved glycaemic control (table 4).[155,156]

Imatinib, a tyrosine kinase inhibitor approved as an antineoplastic agent, when used in a patient with chronic myeloid leukaemia and insulin-treated type 2 diabetes, led to the remission of diabetes (table 4).[157] Later, beneficial effects on β-cell health and function were described.[158–160] Systematic clinical trials have not been reported.

Given the difference in gut microbiota composition between patients with and without type 2 diabetes,[237,238] therapeutic manipulation of the microbiome could be helpful. Faecal microbiota transplantation studies from healthy donors to patients with signs of the metabolic syndrome have shown that insulin sensitivity transiently increases for a duration of 6–18 weeks.[239,240] These findings show that the gut microbiota can influence host metabolic functions and potentially be a novel target for diabetes therapy. Indeed, therapy with prebiotic and synbiotic (poorly digestible carbohydrates or fibre)[241] or probiotic (microorganisms) supplements[242–244] have been found to be associated with improved glycaemic control and lipoprotein profiles. However, more research is needed to investigate the effectiveness of targeting the microbiota of patients with diabetes.

Brown adipose tissue contributes prominently to metabolic rates and energy expenditure. Without stimulation, this type of adipose tissue is not very active in human patients. Hints that cold exposure can activate brown adipose tissue even in human patients has sparked research in elucidating other approaches for its activation with the aim to burn substrates and energy in order to reduce plasma glucose and bodyweight.[245]

Future approaches to the individual choice of glucose-lowering medications will most probably be driven by the phenotypic (eg, by anthropometric or laboratory parameters) or even genotypic characterisation. By cluster analysis, subpopulations with more homogeneous characteristics have been defined, which differ in their susceptibility for certain diabetes complications, but also with respect to diabetes progression (eg, towards needing insulin therapy).[246] The same clusters have been confirmed in other populations,[247] so that they appear to have a generalisable validity. It is likely that optimum treatment will differ between such subgroups, most probably related

Search strategy and selection criteria

We searched the literature accessing PubMed using Endnote. Search terms were: "insulin", "smart insulin", "peroxisome proliferator activator receptor agonists" or "PPAR", "glucagon receptor antagonists", "glucokinase activators", "inhibitors of 11 ß-hydroxysteroid dehydrogenase" or 11ß-HSDH", "adiponectin", "fibroblast growth-factor-21" or "FGF21", "fibroblast growth-factor-1" or "FGF1", "imeglimin", "GPR40", "GPR119", "GPR120", "bile acid receptor", "TGR5" , "GLP-1 peptide receptor agonist(s)", "GLP-1 receptor activator(s)", "glucagon-like peptide-1" or "GLP-1", "glucose-dependent insulinotropic polypeptide" or "GIP", "glucagon", "peptide YY" or "PYY", "dextromethorphan" or "N-methyl-D-aspartate receptors" or "NMDAR", "imatinib", "ranolazine", "brown adipose tissue" or "BAT", "pharmacogenomics" or "pharmacogenetics" (mentioned in the title or abstract), all in connection with "glucose", "insulin", "diabetes" (mentioned in the title or abstract). We screened the retrieved original articles, reviews, and commentaries for additional references. We restricted active searches to the period Jan 1, 2010, to Jan 31, 2021, and to the English and German language. We created the final reference list on the basis of originality and relevance to the topic of the present review.

to the predominant pathophysiology driving their pathogenesis. Genetic traits (eg, allelic polymorphisms of diabetes-related genes) can predict the efficacy of treatment with particular agents; possibly because the genetic trait predicts the absorption, distribution, or elimination (ie, pharmacokinetics), or relates to the core mechanism of action (eg, β-cell mass and function in relation to insulinotropic agents).[248–250] Genetic characteristics can also predict the risk for certain adverse events (eg, hypoglycaemia with sulfonylurea treatment).[248,249] However, tools that would allow to test for a panel of relevant allelic variants at a reasonable price are not yet readily available.

Conclusions

In conclusion, multiple novel mechanisms potentially mediating a reduction in plasma glucose concentrations are being explored. Although not all ideas that sound promising as of today will eventually lead to approved or even widely used diabetes drugs, it seems very probable that some of them will eventually be successful and extend our armamentarium of medications used for the benefit of patients with type 2 diabetes. In our personal judgement , smart insulin preparations, agents addressing impaired mitochondrial function (eg, imeglimin), GLP-1 secretagogues, small molecule oral GLP-1 receptor agonists, and unimolecular peptides interacting with two or three enteroendocrine hormone receptors (above all, GIP and GLP-1 co-agonists and, potentially, GLP-1 and peptide YY agonists) have the greatest potential for supporting a substantial improvement of glycaemic and bodyweight control in the growing population with type 2 diabetes. For other peptide-based approaches (adiponectin, FGF1- and FGF21-based), it will probably take more time to reach approval. In addition, therapeutic approaches to impact on risk factors and comorbidities typically associated with type 2 diabetes, or to address mechanisms leading to diabetes-associated complications (microvascular and macrovascular complications and neoplasms) independent from lowering plasma glucose concentrations or fluctuations, might gain more importance.

Contributors

MAN did the literature search, designed the outline of the manuscript, prepared tables and figures, and wrote the initial draft of the manuscript. JW helped with the literature search, the preparation of figures and tables, and contributed paragraphs to the initial draft. JJM participated in the general outline of the manuscript and gave input regarding critical intellectual content into the revision of figures, tables, and text. All authors approved the final version of the manuscript and decided to submit it for publication.

Declaration of interests

MAN has been a member on advisory boards or has consulted with AstraZeneca, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Menarini/Berlin Chemie, Merck, Sharp & Dohme, and NovoNordisk. He has received grant support from AstraZeneca, Eli Lilly, Menarini/Berlin-Chemie, Merck, Sharp & Dohme, and NovoNordisk. He has also served on the speakers' bureau of AstraZeneca, Boehringer Ingelheim, Eli Lilly, Menarini/Berlin Chemie, Merck, Sharp & Dohme, and NovoNordisk. JJM has received consulting and speaker honoraria from AstraZeneca, Eli Lilly, Merck, Sharp & Dohme, Novo Nordisk, Sanofi, and Servier. He has received research support from Boehringer Ingelheim, Eli Lilly, Merck, Sharp & Dohme, Novo Nordisk, and Sanofi. JW has declares no competing interests.

Acknowledgments

We thank Laura Weilandt for help with retrieving literature.

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