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Tahrani, Abd A.; Barnett, Anthony H.; Bailey, Clifford J.

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Drugs for type 2 diabetes mellitus: pharmacology and implications for therapy

Abd A Tahrani[1,2], Anthony H Barnett[1,2],Clifford J Bailey[3]

[1]Centre of Endocrinology, Diabetes and Metabolism, University of Birmingham, Birmingham, UK

[2]Department of Diabetes and Endocrinology, Heart of England NHS Foundation Trust, Birmingham, UK

[3] School of Life and Health Sciences, Aston University, Birmingham, UK

Corresponding author:

Abd A Tahrani

Department of Diabetes and Endocrinology

Birmingham Heartlands Hospital

Birmingham B9 5SS

Abd.tahrani@nhs.net

+44 7801549960

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Abstract

Type 2 diabetes mellitus (T2DM) is a global epidemic that poses a major challenge to health care systems. Improving metabolic control to approach normal glycaemia (where practical) greatly benefits long-term prognosis and justifies early, effective, sustained and safety-conscious intervention. Greater understanding of the complex pathogenesis of T2DM has underpinned the development of a selection of glucose-lowering therapies with different and complementary mechanisms of action that have expanded treatment options and facilitated an individualised management strategy. Over the last decade several new classes of glucose lowering agents have been licensed including glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium-glucose transporter-2 (SGLT-2) inhibitors. These can be used individually or in combination with previously well-established classes such as biguanides, sulfonylureas and thiazolidinediones. Whilst newer agents may offer advantages which include low risk of hypoglycaemia and help with weight control, their long term safety has to be established. In this review, we assess the pharmacokinetics, pharmacodynamics and safety profiles, including cardiovascular safety, of currently available therapies for the management of hyperglycaemia in patients with T2DM within the context of disease pathogenesis and natural history. In addition, we briefly review treatment algorithms for patients with T2DM and lessons from present therapies to inform the development of future therapies.

Introduction

Type 2 diabetes mellitus (T2DM) is a global epidemic with an estimated worldwide prevalence of 415 million people in 2015, projected to reach 642 million people by 2040[1]. Given its huge health, social, and economic burden[1-3]T2DM presents a major challenge to healthcare systems around the world.

T2DM is a complex endocrine and metabolic disorder in which the interaction between genetic and environmental factors generates a heterogeneous and progressive pathology with variable degrees of insulin resistance, dysfunction of pancreatic β-cells and α-cells and other endocrine disturbances (**Figure 1**)[4-14]. Insulin resistance is due to deficits in the insulin-receptor-postreceptor signalling pathways, and T2DM emerges when β-cells are no longer able to secrete sufficient insulin to overcome insulin resistance[4, 15-17]. Overweight and obesity are major risk factors for the development of insulin resistance via several mechanisms[5, 16, 18-21].

Hyperglycaemia is the cardinal biochemical feature of diabetes, causing increased oxidative and nitrosative stress and the activation of inflammatory pathways and endothelial dysfunction, precipitating microvascular complications and contributing to macrovascular disease, which are major causes of morbidity and mortality[22]. Several randomised controlled trials (RCTs) have shown the short and long term benefits of improving glycaemic control, delaying the onset and reducing the severity of diabetes-related outcomes particularly retinopathy, nephropathy, neuropathy, cardiovascular disease and mortality[23-26]. Hence attaining near normal blood glucose levels (where practical) is a major aim of treatment.

Several strategies are available for this purpose: life style changes including dietary prudence, weight loss and physical activity remain the cornerstones of management, but because of the progressive nature of T2DM and the difficulty in maintaining life style changes long-term , most patients require treatment with oral and eventually injectable treatments[27].

For more than four decades only two classes of oral glucose-lowering medications were available (biguanides and sulfonylureas) but over the last 2 decades there has been significant expansion in the treatment options (**Table 1**)[27, 28]. In this review, we provide an evaluation of the therapies available for the management of hyperglycaemia in patients with T2DM.

Glycaemic control and targets for patients with T2DM

The treatment needs of patients with T2DM and the responses to treatments are highly variable, reflecting the complexity and variability of the pathogenic process[29, 30]and posing difficult decisions regarding choice of therapy and glycaemic targets. Relevant factors include patient age, diabetes

duration, weight, risk of hypoglycaemia, cardiovascular risk, concomitant treatments, presence of diabetes complications and concomitant life-limiting illness. Other factors that are more difficult to quantify in clinical practice for an individual patient include the reserve capacity for insulin secretion, genetic factors that might affect responses to therapies, the risk of developing future complications and the rate of disease progression[31].

The benefits of intensive glycaemic control on long-term diabetes-related complications and mortality are well described, particularly when started promptly after diagnosis in younger, relatively uncomplicated patients[23-26]. However, intensive glycaemic control is not without risks such as hypoglycaemia (dependent on which glucose lowering agents are used), weight gain, and possible increases in cardiovascular events and mortality in high risk individuals. These risks might relate, at least in part to the chosen glycaemic target and the medications [23, 32-37], accounting for a preferred "individualised" rather than a "one size fits all" management strategy[37]. The difficulty is how to identify the patients in whom the risks of intensive glycaemic control outweigh the benefits. Stringent glycaemic control is not advised in older patients or in those with advanced disease, longer diabetes duration, or established cardiovascular disease[28, 37]. An HbA1c target of 7% is commonly quoted in guidelines, a lower target might be appropriate for newly diagnosed younger patients with T2DM and no complications; a higher HbA1c might be more realistic for an elderly or frail patient with a long duration of disease and established complications.

Biguanides

The only biguanide available in clinical practice is metformin (dimethylbiguanide)[38]. Other biguanides (phenformin and buformin) were withdrawn due to risk of lactic acidosis[39]. Biguanides stem from a guanidine-rich herb *Galega officinalis* (French lilac) that was used in traditional medicine in Europe[38, 40] . Metformin was introduced in Europe in 1957 and the USA in 1995, and has since become the most prescribed anti-diabetes agent worldwide[38, 40].

Mechanism of action

Metformin enters cells mainly via the organic cation transporter-1 (OCT-1) and exerts multiple insulin-dependent and independent actions that vary with the level of drug exposure and the control of nutrient metabolism within different tissues (**Figure 2**)[29, 38, 41-43]. The gut is exposed to high concentrations of metformin[43], which interrupt the respiratory chain at complex I and increase glucose utilisation, anaerobic glycolysis and lactate production: the lactate can be partly converted back to glucose in the liver[44]. Increased lactate-glucose turnover contributes to futile cycling and increases energy dissipation, which might assist in the weight neutrality observed in metformin

treated patients[29, 43]. In the liver, metformin increases insulin signalling, reduces glucagon action, and reduces gluconeogenesis and glycogenolysis[29]. [29]Metformin can inhibit the mitochondrial redox shuttle enzyme glycerophosphate dehydrogenase, altering hepatocellular redox state. This is associated with a reduced ATP:AMP ratio, activation of AMP kinase (AMPK) and reduced conversion of lactate and glycerol to glucose, decreasing hepatic gluconeogenesis[45]. . In addition, metformin favours the utilisation of glucose relative to fatty acids as a cellular source of energy in the liver[38]. In muscle, metformin increases insulin-mediated glucose uptake via glucose transporter-4 (GLUT4)[29].

Because delayed release formulations of metformin have achieved similar efficacy at lower doses than 'regular' formulations, it appears that the gut is a major site of metformin action at therapeutic doses[46]. Metformin can increase GLP-1 levels, even in the absence of an oral glucose load and in patients with and without T2DM[47-51]. The mechanisms are not fully elucidated but could include inhibition of sodium-dependent bile acid transporters which increase the availability of ileal bile acids to activate the G-protein-coupled bile acid receptor TGR5 on L-cells. Metformin has also been reported to reduce the activity of DPP-4, and increase GLP-1 secretion via muscarinic (M3) and gastrin-releasing peptide receptor-dependent pathways[47-52]. Metformin may also increase the expression of GLP-1 receptors on pancreatic β cells, mediated by peroxisome proliferator-activated receptor α (PPARα)[50]. The impact of metformin on GLP-1 might contribute to its weight neutral effect and reduction in hepatic glucose output by inhibiting glucagon secretion[47-49]. Metformin also appears to alter the circadian control of liver and muscle glucose metabolism[43].Metformin induced AMPK-activation results in phosphorylation of casein kinase I which leads to the degradation of the circadian clock component, mPer2 which increases the expression of CLOCK and BMAL1 (circadian genes) and causes phase advance in the circadian rhythm in rodents and in vitro studies[53, 54]. A recent study in mice showed that while metformin causes phase advance in the liver, it causes phase delay in the muscle[54], and the effects of metformin on circadian rhythm are blocked in AMPK knock out mice[53].

Pharmacokinetics

Metformin has an oral bioavailability of 40 to 60%, and a plasma half-life ($t_{1/2}$) of 4-9 hours. It is eliminated unchanged in the urine mostly via tubular secretion rather than glomerular filtration[29, 55].[29, 55].

Pharmacodynamics

Metformin is widely used as first-line pharmacotherapy in patients with T2DM, because of its efficacy, long term safety record, low risk of hypoglycaemia, weight neutrality, and favourable impact on vascular disease[37]. It typically reduces fasting plasma glucose (FPG) by 2-4 mmol/L and

HbA1c by 1-2% largely independent of age, weight and diabetes duration as long as some residual β-cell function remains[29, 40]. In the 10 year follow up data from the United Kingdom Prospective Diabetes Study (UKPDS), patients who received metformin had significant risk reductions for any diabetes-related end-point of 21% (P=0.01), diabetes-related death of 30% (P=0.01), and myocardial infarction (MI) of 33% (P=0.005) compared with overweight patients in the conventional-therapy group[24].[29, 56]. Metformin may also be associated with reduced cancer risk in patients with T2DM, particularly prostate, pancreas and breast[29, 43].

Due to the progressive nature of T2DM, the addition of other differently acting glucose lowering treatments (including insulin) might be required[15, 37, 57].Hence, there are many fixed dose combinations of drugs that include metformin.

Safety and adverse events

The main side effect of metformin treatment is abdominal discomfort and other gastrointestinal adverse effects, including diarrhoea[38]. [38]. Symptoms may remit if the dose is reduced, but around 10% of patients cannot tolerate the drug at any dose[38] possibly associated with variants of OCT-1 leading to an increased metformin concentration in the intestine[58]. Concomitant use of drugs that inhibit OCT-1 activity (such as tricyclic antidepressants, citalopram, proton pump inhibitors, verapamil, diltiazem, doxazosin, spironolactone, clopidogrel, rosiglitazone, quinine, tramado, and codeine amongst others) (OR=1.63, 95% CI 1.22-2.17, p=0.001) or the presence two reduced-function OCT-1 alleles compared to carriage of one or no deficient allele (OR=2.41, 95% CI 1.48-3.93, p< 0.001) increased the risk of metformin intolerance (defined as patients who stopped metformin within the first 6 months of treatment)[58].

Metformin is contraindicated in patients with advanced chronic kidney disease, significant liver disease and conditions that might predispose to hypoxia or reduced tissue perfusion. However, observational and database studies indicate that advantage can be taken of the broad therapeutic index with metformin[39, 59, 60] and careful attention to dose has enabled its use even in patients with cardiovascular disease (including mild to moderate heart failure[39, 61]and chronic obstructive pulmonary disease[62]). However it is important to adjust the dose and monitor renal function to ensure that it can be adequately eliminated, and it should be stopped if hypoxaemia occurs[63, 64].

The UKPDS noted that compared with sulfonylureas and insulin in obese patients with newly diagnosed T2DM, metformin use was associated with significantly reduced MI, coronary deaths, and all-cause mortality by 39, 50, and 36%, respectively[65, 66].The 10-year follow up of the UKPDS showed that the reduction in MI and death persisted[24]. Database analyses have consistently provided corroborating evidence[66]. However, increased use of statins and renal protective medications in

recent years makes it difficult to assess the current impact of metformin on cardiovascular disease[66]; several RCTs are ongoing to assess this[66].

Sulfonylureas

Sulfonylureas were developed as variants of sulfonamides after the latter were reported to cause hypoglycaemia[38, 67]. They are classified into first generation (eg tolbutamide, chlorpropamide) and second generation (eg glibenclamide (glyburide), gliclazide, glipizide and glimepiride)[38], the latter having greater potency enabling use at lower doses.

Mechanism of action

Sulfonylureas act directly on the pancreatic β-cells by binding to the cytosolic face of the sulfonylurea receptor SUR1 which is part of the Kir6.2 (K-ATP) potassium efflux channel ,(**Figure 3**)[38, 68]. In vitro studies show that persistent exposure to sulfonylureas for several days can desensitise the β-cells and reduce the insulin secretory response. However, studies in patients with T2DM have shown that a 25% increase in 24 hour insulin secretion with glibeclamide is maintained for 6-10 weeks, but efficacy usually declines after 6-12 months of sulfonylurea therapy during clinical trials[69].

Pharmacokinetics

Sulfonylureas vary considerably in their pharmacokinetic properties (**Table 2**)[38, 69-71]. They have high bioavailability and reach peak plasma concentrations within 1.5-4 hours[69]. They are metabolized in the liver to varying extents to a range of active and inactive metabolites that are eliminated along with unchanged drug via the bile and urine (**Table 2**); hence caution is needed in patients with hepatic and / or renal impairment[38]. Half-lives are <10h for most members of the class, but extend to >24h with chlorpropamide. Therapeutic effects are much longer than the half-lives where active metabolites are formed [69].. In general first generation sulphonylureas should be avoided in patients with chronic kidney disease (CKD) stages 3, 4 and dialysis. Gliclazide and glipizide can be used in patients with CKD and/or dialysis without extensive dose adjustment[72-74]. Glimepiride can be used in patients with CKD but not dialysis but with low dose initiation and careful titration[72, 74].

Sulphonylureas are highly bound to plasma proteins (>90%) which can lead to interactions with other protein-bound drugs such as salicylates, sulfonamides and warfarin[38, 69].

Some medications potentiate the glucose lowering effects of sulfonylureas by either reducing their hepatic metabolism (e.g. some antifungals and MAOIs), displacing sulfonylureas from plasma protein binding (e.g. coumarins, NSAIDs, sulfonamides), decreasing excretion (e.g. probenecid) or by

antagonising their mechanism of action (e.g. diazoxide and other K-ATP channel openers)[38]. Drugs that induce sulfonylurea metabolism (e.g. rifampicin) reduce the glucose lowering effects[38].

Altered formulations of some sulfonylureas enable quicker onset of action (e.g. micronized glibenclamide in the USA) or a longer action (e.g. extended release glipizide and gliclazide modified release) but maintain similar glucose lowering efficacy[38, 75-77].

Pharmacodynamics

As monotherapy, sulfonylureas lower FPG by 2–4 mmol/L and HbA_{1c} by 1–2%[29, 38, 69, 71]. However, the failure rates of sulfonylureas as monotherapy are greater than those of metformin or rosiglitazone[15].. Sulfonylureas can be used as first-line treatment in patients intolerant to metformin or can be used in combination with most other glucose lowering medications except meglitinides which have a similar mechanism of action[29, 38]. In patients with a greater reserve of β-cell function sulfonylureas can produce a greater and longer response[38].

Safety and adverse events

Hypoglycaemia and weight gain are the main side effects of sulfonylureas. Weight gain of 1–4 kg that stabilizes after about 6 months is common following drug initiation[29]. Weight gain is most likely related to the anabolic effect of increased insulin and reduced glycosuria[28, 29, 78].

Hypoglycaemia has been reported in 20-40% of patients receiving sulfonylureas and severe hypoglycaemia (requiring third party assistance) occurs in 1-7% of patients[29, 38, 79] but this varies between studies depending on the population examined , the definition of hypoglycaemia and the type and pharmacokinetics of the sulphonylurea[75]. In a study from six UK secondary care centres, self-reported hypoglycaemia prevalence was 39%(95% CI 30 to 49%) which was similar to the prevalence of self-reported hypoglycaemia in patients withT2DM who were insulin treated for less than 2 years[79]. The prevalence of self-reported severe hypoglycaemia was 7% (3 to 13%)[79]. Continuous glucose monitoring (CGM) showed that 22% (95%CI 15 to 31%) had at least one episode of interstitial glucose< 2.2 mmol/L which was also similar to patients with T2DM using insulin for < 2 years[79]. The study confirmed that longer acting sulfonylureas with active metabolites are more likely to cause hypoglycaemia[29, 38], and that older people, those living alone and those with renal or liver impairment require extreme caution with sulfonylureas as do car drivers[29, 38]. Education and glucose self-monitoring are essential in patients receiving sulfonylureas; an RCT in patients receiving gliclazide modified release showed that self-monitoring of blood glucose reduced the risk of symptomatic hypoglycaemia and increased HbA1c reductions compared to no monitoring[80].

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The cardiovascular safety of sulfonylureas is still controversial. In the 1970s the University Group Diabetes Program raised concerns regarding increased cardiovascular disease risk with tolbutamide[81] and since then many database studies, mostly retrospective, have suggested that sulfonylureas (particularly glibenclamide) are associated with less benefit than metformin against cardiovascular disease in patients with T2DM[66]. However, RCTs such as UKPDS, ADVANCE and ACCORD did not show an increase in CVD mortality or morbidity in sulfonylurea-treated patients[66]. The ongoing CAROLINA study comparing linaglitpin to glimepiride might help address some of the cardiovascular safety issues.

Meglitinides

The two main meglitinides (or glinides) are nateglinide and repaglinide. The class takes its name from the meglitinide moiety of glibenclamide which exerts an insulin releasing effect independently of the sulfonyl moiety[27, 29, 82].

Mechanism of action

Meglitinides bind to the benzamido site on the SUR1 on β-cells, which is separate from the sulfonyl binding site but results in a similar effect on the Kir6.2 channels (**Figure 3**)[38]. However, the more rapid and shorter duration of action of meglitinides suits use as prandial glucose lowering agents [38].

Pharmacokinetics

Repaglinide is almost completely absorbed with peak plasma concentrations after about 1 hour. It is highly protein bound, quickly metabolized in the liver, mostly by CYP3A4 to inactive metabolites, which are mostly excreted in the bile. The plasma half-life of ~1h [38, 83, 84] making it suitable for use in patients with poor renal function. Taken about 15 minutes before a meal, repaglinide produces a prompt insulin response which lasts about 4-6 hours[38]. Bioavailability is unaffected by food. Drugs that inhibit CYP3A4 (eg ketoconazole, anti-bacterial agents, steroids and cyclosporine) may increase repaglinide concentrations, while drugs that induce CYP3A4 (eg rifampicin, carbamazepine, and barbiturates) may accelerate its metabolism[84, 85].

Nateglinide has a slightly faster onset and shorter duration of action (3-5 hours), is highly protein bound, metabolised in liver by CYP3A4 (same interactions as repaglinide) and mostly excreted in the urine[38, 84].

Pharmacodynamics

Repaglinide (0.5–4 mg) or nateglinide (60–180 mg) taken before meals produce dose-dependent increases in insulin concentrations and reduce post-prandial and fasting hyperglycemia[38].

Meglitinides are usually used in combination with metformin, a thiazolidinedione or insulin, although they can be used as monotherapy. RCTs have shown that HbA1c reductions are similar or slightly less than observed with sulfonylureas when used as monotherapy or as add-on to metformin (an additional 0.5–1.5%)[38, 84]. Repaglinide can be used effectively in conjunction with basal and biphasic insulins[86, 87]. In a 12-month RCT, non-obese patients with T2D for 10 years were randomised (n=102) to either repaglinide or metformin added to biphasic insulin aspart 30/70 which was titrated to achieve HbA1c < 6.5%. At the end of treatment, HbA1c reductions were similar in both treatment groups (baseline vs. study-end HbA1c: 8.15±1.32 vs. 6.72±0.66% and 8.07±1.49% vs. 6.90±0.68% for the metformin and repaglinide respectively; P=0.2 for between groups difference)[87].

In a head-to-head RCT, in which 150 drug-naïve patients were randomised to either repaglinide (0.5 mg/meal, maximum dose 4 mg/meal) or nateglinide (60 mg/meal, maximum dose 120 mg/meal) for 16 weeks, HbA1c reductions from an average 8.9% at baseline were greater for repaglinide than nateglinide (-1.57 vs. -1.04%; P = 0.002)[88].FPG reductions were also greater with repaglinide vs. nateglinide (-57 vs. -18 mg/dL; P < 0.001)[88].

Meglitinides are suited to patients with irregular meal patterns or older patients at increased risk of hypoglycaemia[38].

Safety and adverse events

Studies with repaglinide and nateglinide report variable rates of hypoglycaemia – similar to sulphonylureas – and generally less weight gain[84, 90-94]. In the head-to-head RCT described above hypoglycaemia (blood glucose <50 mg/dl) was more common in repaglindide treated patients compared to nateglinide (7% vs. 0%)[88]. The weight gain was also slightly greater in the repaglinide group (1.8 vs. 0.7 kg)[88]. When added to biphasic insulin and compared to metformin repaglinide resulted in similar hypoglycaemia but the weight gain was less with metformin (difference in mean body weight -2.51 kg, 95% CI -4.07 to -0.95)[87].

Meglitinides can bind to SUR2a/b which are expressed by cardiovascular tissues[84, 95].. In the large RCT , NAVIGATOR, nateglinide did not alter cardiovascular outcomes in people with impaired glucose tolerance with either cardiovascular disease (CVD) or at increased risk of CVD[96]. Repaglinide was not associated with increased CVD or an adverse cardiovascular risk profile in the small studies to date[66, 84, 97].

α-Glucosidase inhibitors (AGIs)

Acarbose was the first AGI to be introduced in early 1990s; subsequently, miglitol and voglibose were introduced in some countries. The class is widely used amongst Asian populations with a diet in which complex carbohydrate predominates[38].

Mechanism of action

AGIs competitively inhibit α-glucosidase enzymes in the brush border of enterocytes lining the intestinal villi, preventing the enzymes from cleaving disaccharides and oligosaccharides into monosaccharides[38, 98]. This delays carbohydrate digestion and defers absorption distally along the intestinal tract, which reduces blood glucose excursions and lowers prandial insulin levels[38]. Passing more glucose further along the ileum can increase GLP-1 and reduce GIP secretion[99]. [100]. Different AGIs have different affinities for the various α-glucosidase enzymes which result in different activity profiles (e.g. acarbose has greatest affinity for glycoamylase whereas miglitol is a stronger inhibitor of sucrase)[38].

Pharmacokinetics

Acarbose is degraded by amylases and bacteria in the small intestine; less than 2% of the unchanged drug is absorbed along with some of the intestinal degradation products. Absorbed material is mostly eliminated in the urine within 24 hours[38]. Miglitol is almost completely absorbed and eliminated unchanged in the urine[38].

Pharmacodynamics

Typical HbA1c reductions are about 0.5%, mostly through reductions in postprandial glycaemia, and depend upon the amount of complex carbohydrate in the diet[29]. In a non-inferiority RCT of Chinese patients (n=784) with newly diagnosed T2DM and mean HbA1c of 7.5%, acarbose resulted in HbA1c reductions similar to metformin (-1.1%, within groups difference 0·01%, 95% CI -0·12 to 0·14%)[101]. However, tolbutamide resulted in greater HbA1c reductions compared to acarbose in newly diagnosed drug-naïve patients with T2DM (n=96, mean baseline HbA1c approximately 8%) (-1.1% vs. 1.8%;mean difference 0.6%, 95% CI 0.2 to 1.0)[102]. Tolbutamide had a greater effect on FPG than acarbose while the impact on PPG was similar[102].

Safety and adverse events

Gastrointestinal side effects of AGIs (flatulence, abdominal discomfort, diarrhoea) are commonly encountered and these can lead to treatment withdrawal. Hypoglycaemia is uncommon: AGIs do not cause weight gain and there are no clinically significant drug interactions.

The STOP-NIDDM RCT noted that acarbose reduced the risk of developing T2DM, delayed the onset of hypertension and reduced macrovascular events by 49% compared to placebo; but the total number of events was too small (n=47) to draw firm conclusions[66, 103, 104]. A large RCT assessing the impact of acarbose on cardiovascular outcomes is ongoing[105].

Thiazolidinediones (TZDs)

Two thiazolidinediones, pioglitazone and rosiglitazone, have varying availability: troglitazone, introduced in 1997, was withdrawn soon after due to idiosyncratic hepatotoxicity [29]. Rosiglitazone and pioglitazone were introduced in 1999: rosiglitazone was discontinued in Europe and its use was restricted in the USA in 2008 after reports of increased cardiovascular risk, and pioglitazone was discontinued in 2011 in some European countries pending enquires into a possible increased risk of bladder cancer.

Mode of action

TZDs are agonists of the peroxisome proliferator-activated receptor-gamma (PPAR-γ) which is a nuclear receptor highly expressed in adipose tissue, and to a lesser extent in muscle, liver, β-cells, vascular endothelium, and macrophages[38, 106]. PPAR-γ activation alters gene expression to promote adipogenesis, insulin sensitivity and tissue glucose uptake, reduce inflammation and alter energy balance (**Figure 4**)[106, 107]in a tissue-specific manner (**Table 3**). PPAR-γ activation reduces hepatic gluconeogenesis, modifies the blood lipid profile and possibly improves β-cell viability[106, 107]. Differentiation of pre-adipocytes into new small insulin sensitive adipocytes by PPAR-γ activation reduces circulating FFA which reduces ectopic lipid accumulation in skeletal muscle and liver and rebalances the Randle (glucose-fatty acid) cycle in favour of glucose utilization by restricting FFA availability as an energy source for hepatic gluconeogenesis[29].

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Pharmacokinetics

TZDs reach peak plasma levels within 1-2 hours [38]. They are almost completely bound to plasma proteins, but their concentrations are not sufficient to interfere with other protein-bound drugs[38]. Pioglitazone is metabolised by CYP2C8 and CYP3A4 to weakly active metabolites that are eliminated via the bile whereas rosiglitazone is metabolised by CYP2C9 and CYP2C8 to inactive metabolites and excreted via the urine[38, 108]. Rifampicin significantly decreases while gemfibrozil increases concentrations of rosiglitazone and pioglitazone [108].

Pharmacodynamics

Maximal doses of TZDs have reduced HbA1c by 0.7-1.6% in RCTs when used as monotherapy or as add-on to metformin, sulfonylureas or insulin [106, 109]. [106].In a RCT, patients with T2DM receiving metformin (n=630, mean age approximately 56 years, mean diabetes duration about 5.5 years, baseline mean HbA1c 8.5-8.7%) were randomised to either pioglitazone or gliclazide as add-on treatment. After 2 years the changes in HbA1c were similar in the pioglitazone and gliclazide arms (0.89% and 0.77% with pioglitazone and gliclazide, respectively, p= 0.2 for between groups difference); while pioglitazone resulted in greater reductions in FPG (1.8 vs. 1.1 mmol/l, p <0.001)[110]. In another RCT, patients with T2DM receiving a sluphonylurea (n=639, mean age approximately 60 years, mean diabetes duration about 7 years, baseline mean HbA1c 8.8%) were randomised to either pioglitazone or metformin as add-on treatment. After 2 years the changes in HbA1c were similar in the pioglitazone and metformin arms (1.03% vs. 1.16%with pioglitazone and gliclazide, respectively, p= 0.17 for between groups difference); the reductions in FPG (around 2 mmol/l) were also similar in pioglitazone and metformin treated patients[110]. Onset of the glucose lowering effect of TZDs is gradual taking 2-3 months to reach maximum effect[38]. The ADOPT trial, in which 4360 patients with T2DM (mean age 56-58 years, baseline HbA1c 7.4%, mostly under 2 years duration) were randomised to glyburide, metformin or rosiglitazone, showed that rosiglitazone has a more prolonged impact on glycaemic control (HbA1c and FPG) as monotherapy compared to metformin or glyburide over 5 years [15]. The glucose lowering efficacy of TZDs seems to vary considerably amongst individuals and there are no definite predictors to identify responders versus non-responders[30].

Safety and adverse events

TZDs do not increase the risk of hypoglycaemia when used as monotherapy or in combination with metformin. Oedema (often identified through rapid weight gain) has been reported in 4-6% of patients receiving TZDs[106] : increased fluid retention is due to increased renal sodium reabsorption through increased expression of sodium channel transporters by collecting duct epithelium[29]. TZDs are associated with weight gain of 2-3 kg for each 1% drop in HbA1c whether used as monotherapy or in combination with metformin or insulin [106]. The weight gain is usually due to increased subcutaneous adipose tissue while visceral fat is either reduced or unaltered[106, 111]. In the ADOPT trial the weight gain with rosiglitazone over 5 years was greater than with glibenclamide (glyburide) (treatment difference 2.5 , 95%CI 2-3.1 kg, p<0.001), while the increase in waist circumference was similar (0.77, -0.21 to 1.76 cm, p=0.12)[15].

RCTs and observational studies show that long term treatment with TZDs lowers bone density and doubles the risk of fractures in patients with T2DM, particularly in women[112]. Similarly, in the ACCORD trial women who received TZDs had double the risk of non-spinal fracture compared to those not using TZDs; this risk was reduced after discontinuation of TZDs[113]. A recent meta-analysis of RCTs showed that TZDs reduced bone mass density at the lumbar spine (difference -1.1% (95% CI -1.6, -0.7); $p < 0.0001$), total hip (-1.0% (-1.4, -0.6); $p < 0.0001$), forearm (-0.9% (-1.6, -0.3); $p = 0.007$) and femoral neck (-0.7% (-1.4, 0.0); $p = 0.06$) which was not reversible after 1 year of stopping treatment in some studies[114].

The cardiovascular safety of TZDs was questioned by a controversial meta-analysis showing that rosiglitazone increased adverse cardiovascular outcomes, and this prompted withdrawal in Europe and restricted use in the USA[66, 115]. However, when the FDA re-examined the data from the RECORD study no significant increase in cardiovascular risk was found[66, 116].

Pioglitazone is a ligand for PPARα through which it appears to reduce several lipid cardiovascular risk factors such as increasing plasma HDL-cholesterol reducing plasma triglyceride reducing small dense LDL-cholesterol particles and increasing larger, more buoyant particles. TZDs can also reduce BP and improve endothelial function ,[66] but rosiglitazone increases plasma LDL-cholesterol and triglyceride [66].

In the PROACTIVE trial, pioglitazone was associated with a numerical but non-significant reduction of the composite outcome of all-cause mortality, non-fatal MI, stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle (HR 0·90, 95% CI: 0·80–1·02, p=0·095). However, pioglitazone significantly lowered the secondary end-point of composite of all-cause mortality, non-fatal MI, and stroke (HR 0·84, 95%CI: 0·72–0·98, p=0·027)[33]. In addition, pioglitazone reduced the risk of subsequent MI and recurrent stroke by 16% and 47% respectively[66, 117, 118]. Nonetheless, the risk of heart failure was higher in the pioglitazone group in the PROACTIVE trial, although this was not associated with increased mortality[66].

However, both rosiglitazone and pioglitazone can cause congestive heart failure in patients who already have diastolic dysfunction due to the propensity for oedema[66]: Effects of rosiglitazone on coronary artery disease are uncertain, but pioglitazone may reduce coronary disease[66, 119-123].

Dipeptidyl peptidase-4 (DPP-4) inhibitors

First introduced in 2007 the currently available DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin)[124]are licensed as monotherapy, dual therapy, triple therapy and in combination with insulin but there are some minor variations in licensing between agents. In addition, once weekly DPP-4 inhibitors (omarigliptin and trelagliptin) are licensed in Japan[125, 126].

Mechanism of action

By inhibiting the enzyme DPP4, DPP-4 inhibitors increase circulating incretin hormones, notably glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). The incretin effect refers to an ability of intestinal factors to enhance nutrient-induced insulin responses during feeding by 50–70% in healthy individuals[127, 128], but this effect is much diminished in T2DM. GIP is secreted by K-cells in the duodenum and jejunum in response to ingestion of carbohydrates and lipids[129-131]. It also reduces gastric acid secretion, plays a role in adipogenesis and possibly β-cell proliferation[129, 131-134]. GLP-1 is secreted from L-cells in the distal ileum and colon[129, 131] and accounts for most of the incretin effect [129, 135] including increased insulin biosynthesis[136, 137]. Additionally GLP-1 reduces glucagon secretion and has several extra-pancreatic actions that enhance satiety and delay gastric emptying (**Figure 5**)[128, 135, 138-140].

GIP and GLP-1 are rapidly degraded by DPP-4[129] which cleaves the N-terminal dipeptide when there is an alanine (as with the incretins) or proline at position N2 [131]. DPP-4 is free in the circulation and also attached to endothelial cells[131, 141] and is widely expressed in human tissues including in the intestine and portal system[131]. The majority of GLP-1 and GIP is therefore inactivated almost immediately following secretion which accounts for a half-life of < 2 min and 5-7 minutes respectively[129, 131, 142, 143]. DPP-4 inhibition results in a 2-3 fold increase in post meal active GLP-1 levels[144, 145]. Unlike GLP-1 receptor agonists (GLP-1 RAs), which are equivalent to a >10 fold increase in GLP-1, DPP-4 inhibitors do not delay gastric emptying or increase satiety and weight loss but avoid initial nausea/vomiting[146, 147].

Pharmacokinetics

The pharmacokinetics of currently available DPP-4 inhibitors are summarised in **Table 4**[124, 148-152]. They produce 77-99% inhibition of DPP-4 activity and are appropriate for once daily dosing except vildagliptin (twice daily), and omarigliptin and trelagliptin (once weekly). They are all predominantly excreted in the urine except linagliptin; hence linagliptin does not require dose adjustment in patients with chronic kidney disease.

DPP-4 inhibitors show little or no interactions with other glucose-lowering agents or other drugs commonly used in patients with T2DM[124, 153], possibly because DPP-4 inhibitors are neither inducers nor inhibitors of CYP isoforms and are not significantly bound to plasma proteins [153]. However saxagliptin, is metabolized to an active metabolite by CYP3A4/5[124, 153].

Pharmacodynamics

On average DPP-4 inhibitors reduce postprandial glucose (PPG) excursions by about 3 mmol/L and FPG by about 1–1.5 mmol/L[29, 124]. A recent meta-analysis assessed the efficacy of DPP-4 inhibitors as monotherapy or as add-on therapy to other oral agents[154]. The meta-analysis included placebo- or active- controlled RCTs of DPP-4 inhibitors (n=98 trials, 24163 patients) of 12-54 weeks duration, and with at least 30 patients in each treatment arm. The mean ages of the participants in the studies included in the meta-analysis were 5-62 years (except two studies with a mean age 72-75 years)[154]. 88 trials of the 98 included were double blinded while the remaining 10 were open label design. The results showed that DPP-4 inhibitors reduce HbA1c by −0.77% (95% CI −0.82 to −0.72%) from an average baseline of 8.05%[154]. In RCTs with a duration of 52-54 weeks (n=18) DPP-4 inhibitors resulted in HbA1c reductions of −0.84%(95%CI −0.99 to −0.68, p=<0.0001); while in RCTs of 12-18 weeks (n-26) the HbA1c reduction was −0.68 (95%CI −0.75 −0.61, p<0.0001)[154].The HbA1c reductions were largely similar across the class but direct head-to-head trials are limited. In this meta-analysis the HbA1c reductions based on the DPP-4 inhibitor used were as follows: vildagliptin 50 mg (n=26, age 56.3 years, baseline HbA1c 8.06%) −0.88%(95%CI −1.00 to −0.75, p=<0.0001); Sitagliptin 100 mg (n=37, age 55.2 years, baseline HbA1c 8.05%) −0.79%(95%CI −0.87 to −0.71, p<0.0001); Saxagliptin 5 mg (n=13, age 55.4 years, baseline HbA1c 8.01%) −0.70%(95%CI −0.79 to −0.62, p<0.0001); Linagliptin 5 mg (n=13, age 59.0 years, baseline HbA1c 8.05%) −0.55% (95%CI −0.65 to −0.45, p<0.0001);Alogliptin 25 mg (n=11, age 55.2 years,baseline HbA1c 8.14%) −0.76% (95%CI −0.86 to −0.66, p<0.0001)[154]..The reductions in HbA1c were greater amongst patients with higher baseline HbA1c (> 9.0%)[154].For RCTs with basal HbA1c <7.5% (n=8, age= 57.4 years, baseline HbA1c 7.32%) HbA1c reduction was −0.63% (95%CI −0.78 to −0.48, p<0.0001); for basal HbA1c 7.5–8.0% (n=28, age 57.6 years, baseline HbA1c 7.82%) −0.70%(95%CI −0.76 to −0.63, p<0.0001); basal HbA1c 8.0–8.5% (n=34, age 55.9 years, baseline HbA1c 8.15%) −0.72% (95% CI −0.79 to −0.64, p<0.0001); basal HbA1c >9.0% (n=30, age 54.2 years, baseline HbA1c 8.63%) −0.93% (95%CI −1.02 to −0.84, p<0.0001)[154]..

Another meta-analysis (27 reports of 19 studies including 7136 patients) showed that DPP-4 inhibitors were associated with a smaller decline in HbA1c compared with metformin when used as monotherapy (weighted mean difference 0.20%, 95% CI 0.08 to 0.32) and GLP-1 agonists (weighted mean difference 1.82%, 95% CI 1.50 to 2.21) and sulphonylureas (weighted mean difference 0.07%,

95% CI 0.03 to 0.11) when used as add-on to metformin[155]. In addition, DPP-4 inhibitors were similar to pioglitazone in reducing HbA1c when used as add-on to metformin (weighted mean difference 0.09%, 95%CI −0.07 to 0.24)[155]. This meta-analysis included RCTs in which four DPP-4 inhibitors (vildagliptin, sitagliptin, saxagliptin, linagliptin) were compared to metformin monotherapy or to sulphonylurea, pioglitazone, GLP-1 receptor agonist or basal insulin as add-on to metformin[155]. For studies comparing DPP-4 inhibitors to metformin monotherapy the trials duration was 24-206 weeks, and the participants had a mean diabetes duration of 1-4.4 years and mean HbA1c of 7.2-9.6%. For add-on to trials the mean diabetes duration for study participants was 5-7.3 years and mean HbA1c of 7.3-8.5%[155].

The comparison of the efficacy of DPP-4 inhibitors to sulphonylureas is complicated by multiple factors including the study-duration, renal function, and the sulphonylurea used as the active comparator[156]. In a meta-analysis of 12 RCTs of at least 18 weeks duration that compared sulphonylureas to DPP-4 inhibitors head-to-head, the mean changes from baseline in HbA1c were modestly but significantly smaller with DPP-4 inhibitors compared with sulfonylureas (difference of mean changes in HbA1c for sulfonylureas-DPP-4 inhibitors: of 0.105 and 95% CI 0.103 to 0.107, $p < 0.0001$)[156]. However, several RCTs of 1-3 years duration showed that DPP-4 inhibitors and sulphonylureas resulted in similar HbA1c reductions[151, 156-165].

The glucose-lowering efficacy of DPP-4 inhibitors is greater in Asian patients with T2DM compared to other ethnic groups (between-group HbA1c difference was -0.26% (95% CI -0.36, -0.17, $p < 0.001$) and might be affected by genetic factors such as the TCF7L2 gene variant[166, 167]. A meta-analysis of RCTs of at least 76-weeks duration suggest that the impact of DPP-4 inhibitors was not durable and lessened during the second year of treatment[168].

Head to head comparisons of DPP-4 inhibitors

Head-to-head trials comparing DPP-4 inhibitors are limited. One RCT that compared saxagliptin to sitagliptin as add-on treatment to metformin in 810 patients (age 58.4 years, diabetes duration 6.3 years, baseline hbA1c 7.7%) showed that HbA1c reductions over 18 weeks were similar between both treatments (adjusted mean changes in HbA1c: - 0.52 and - 0.62%; between-group difference 0.09% (95% CI - 0.01 to 0.20%)[169]. However, sitagliptin resulted in a slightly greater reduction in FPG (− 0.60 mmol/L vs. − 0.90 mmol/L for saxagliptin vs. sitagliptin respectively; treatment difference 0.30 mmol/L (95% CI, 0.08–0.53 mmol/L))[169].

In another RCT 148 patients with T2DM and eGFR < 30 ml/min/1,73m^2 who were either drug naive or treated with any glucose-lowering agents were randomised to vildagliptin 50 mg or sitagliptin 25 mg once daily[170].Both treatments resulted in similar reductions in HbA1c over 24 weeks (adjusted

mean change in HbA_{1c} was −0.54% from a baseline of 7.52% with vildagliptin vs. −0.56% from a baseline of 7.80% with sitagliptin, p = 0.874). Vildagliptin lowered FPG by 0.47 ± 0.37 mmol/l while FPG increased in the sitagliptin group by 0.16 ± 0.43 mmol/l but the difference between groups was not statistically significant (p= 0.185)[170].

In a phase 3 non-inferiority RCT 243 T2DM patients inadequately controlled by diet and exercise were randomly assigned to receive trelagliptin (100 mg once weekly), alogliptin (25 mg daily), or placebo for 24 weeks[171]. Trelagliptin was non-inferior to alogliptin and resulted in similar reductions in HbA1c (-0·33% vs. -0.45% for trelagliptin and alogliptin respectively; least squares mean difference 0·11% (95% CI -0·054 to 0·281)). Both trelagliptin and alogliptin significantly reduced mean HbA1c compared with placebo (p<0·0001)[171].

In another RCT, 412 patients with T2DM, drug naïve or on oral glucose lowering treatments, were randomised to omarigliptin 25mg weekly, sitagliptin 50mg daily and or placebo for 24 weeks[172]. At baseline, randomized patients had a mean HbA1c of 7.9, 8.0 and 8.1% in omariglitpin, sitagliptin and placebo respectively[172]. Omarigliptin resulted in HbA1c reductions of -0.66% (-0.76 to -0.57) which was singficantly greater than placebo (p< 0.001) and similar to sitagliptin (least squares mean change -0.02%, 95% CI -0.15 to 0.12) and met the pre-specified non-inferiority criterion[172].

Safety and adverse events

DPP-4 inhibitors are generally well tolerated and the incidence of adverse events is similar to placebo and lower than other glucose lowering agents[155, 173]. The incidence of gastrointestinal symptoms is lower with DPP-4 inhibitors than metformin or a GLP-1 receptor agonist[155]. The risk of hypoglycaemia in DPP-4 treated patients is very low except when combined with sulfonylureas or insulin[124, 155, 173].

DPP-4 has many substrates other than incretins including bradykinin, enkephalins, neuropeptide Y, peptide YY1–36, gastrin releasing polypeptide, substance P, insulin-like growth factor I, vasostatin 1, the α chains of thyrotropin, luteinizing hormone, chorionic gonadotropin and several chemokines such as monocyte chemotactic protein 1 (MCP-1)[174]; however no adverse impacts have been observed in clinical trials[29, 124, 149]. In addition, DPP-4 is the CD26 T-cell activation antigen, but neither CD26 knockout mice nor the DPP-4-specific inhibitors used in animals or humans have shown any significant untoward immune-related effects[29].

Several meta-analyses and pooled analyses have shown that DPP-4 inhibitors (individually and as a class) were associated with reductions in cardiovascular events[66, 175]. However, these studies were retrospective and not specifically designed to examine the effect of DPP4 inhibitors on CVD

incidence[66]. Three recent RCTs, SAVOR-TIMI, EXAMINE and TECOS confirmed that saxagliptin, alogliptin and sitagliptin respectively were not associated with increased risk of adverse cardiovascular outcomes[66, 176-179]. The populations studied in these trials were each slightly different. The SAVOR-TIMI study included patients with T2DM with a previous cardiovascular event or at increased risk of cardiovascular disease. EXAMINE included patients with T2DM and an acute MI or hospitalization for unstable angina in the prior 15–90 days. TECOS included patients with T2DM who were above 50 years old and had established cardiovascular disease.

These studies were designed to look specifically at the effect of the DPP-4 inhibitors on cardiovascular safety so that patients in the placebo arm received other glucose-lowering therapies to minimise any differences in HbA1c between the two arms. In the SAVOR-TIMI study saxagliptin treatment was associated with a 3.5% incidence of hospitalization for heart failure vs. 2.8% in the placebo arm (P = 0.007), without an increase in mortality, and this increase was independent of baseline renal function although saxagliptin reduced microalbminuria[66, 176, 177]. The heart failure effect was not observed in EXAMINE or TECOS and the reason for that finding in patients treated with saxagliptin remains unclear. An ongoing study (CAROLINA) is examining the impact of linagliptin vs. active comparator (glimepiride) rather than placebo on cardiovascular outcomes.

The SAVOR-TIMI, EXAMINE and TECOS trials did not show statistically significant increased risk of pancreatitis or pancreatic cancer in patients using DPP-4 inhibitors [176-180]; however, a meta-analysis of these three RCTs showed a statistically significant increased risk of acute pancreatitis in patients using DPP-4 inhibitors (OR 1.82, 95%CI 1.17, 2.82, p=0.008)[181]

GLP-1 receptor agonists (GLP-1 RAs)

Exenatide (twice-daily) was the first GLP-1 RA, introduced in 2005. Since then two once-daily (liraglutide and lixisenatide) and three once-weekly (exenatide QW, albiglutide and dulaglutide) have become available to use in combination with oral glucose lowering agents and basal insulin (except Exenatide QW is not licenced to be used with basal insulin). Dulaglutide and albiglutide are also licenced as monotherapy in patients who are intolerant to metformin.

Exenatide (synthetic exendin-4), a peptide originally isolated from saliva of the lizard *Heloderma suspectum* (Gila monster)[129, 182],shares 53% homology with human GLP-1 and contains an Ala 8 – Gly substitution for resistance to degradation by DPP-4[129, 183]. Exenatide QW sustained release has embedded exenatide within biodegradable polymeric microspheres of poly D L lactic-co-glycolic acid[184]. Liraglutide is a true analogue of GLP-1 with a 16 carbon fatty acid chain attaching Lys 26 to albumin to mask the DPP-4 cleavage site[185]. Albiglutide has two copies of GLP-1 in series, each with

an Ala 8-Gly substitution and fused to albumin[186]. Lixisenatide is an exendin-4 analogue with six Lys residues added at the C-terminus to confer resistance to DPP-4[187]. Dulaglutide has two copies of a GLP-1 analogue (Gly8, Glu22, Gly36) covalently linked to an Fc fragment of human IgG4[188].

Mechanism of action

GLP-1 RAs activate the GLP-1 receptor and hence mimic GLP-1 (**Figure 3&5**) contributing to reductions in fasting and post-prandial glycaemia and weight loss [189]. However, the therapeutic concentrations of the GLP-1 RAs are far higher than physiological GLP-1 levels, and while GLP-1 deficiency has been described in patients with T2DM this is not a universal characteristic of the disease[189].

Pharmacokinetics

The pharmacokinetics of GLP-1 RAs are summarised in **Table 5**. GLP-1 RAs are delivered by subcutaneous injection. Exenatide twice daily is rapidly absorbed[190]. T-max is about 2 h, half-life is 3-4 h[190] and elimination is mostly renal by glomerular filtration and proteolytic degradation[191-193]. Exenatide clearance is decreased by 36 and 84 % in patients with moderate and severe renal disease, requiring caution and discontinuation in moderate and severe renal disease respectively[194]. The once-weekly formulation reaches therapeutic levels within 2 weeks and maximum concentrations by 6 weeks[195]. Liraglutide half-life is 10-15 hours with maximum plasma concentrations at 9–12 h[196-198]. Lixisenatide has a half-life of 2–4 hours and peak concentrations at 1-2 hours[199]and exerts its main effect on the meal immediately after injection. Albiglutide reaches peak concentrations by 3–5 days and the half-life is 6-7 days[200]. Dulaglutide achieves maximal plasma concentration by 12-72 h and steady-state by 2 weeks [201]. The mean plasma half-life is ~ 4 days[201]. GLP-1 RAs are not recommended in severe renal disease; they have limited drug interactions but can affect the rate and extent of availability of other medicines such as acetaminophen (paracetamol) and statins due to the delay in gastric emptying (except exenatide QW in which delayed gastric emptying is minor)[28, 202].

Pharmacodynamics

The efficacy of GLP-1 RAs was explored in large programmes of placebo-controlled and active comparator RCTs summarised in **Tables6 and 7**; including AMIGO (exenatide) Diabetes Management for Improving Glucose Outcomes); LEAD (Liraglutide Effect and Action in Diabetes); DURATION (Diabetes therapy Utilisation: Researching changes in HbA1c weight and other factors Through Intervention with exenatide ONce-weekly); AWARD (Assessment of Weekly AdministRation of LY2189265 (dulaglutide) in Diabetes), GETGOAL for lixisenatide and HARMONY for albiglutide[203-240].

Impact on glycaemic measures

Exenatide significantly reduced measures of glycaemic control when used as mono- or add-on therapy (**Table 6**)[241-245]. A meta-analysis of RCTs in which exenatide BD was used as add-on to existing metformin therapy for 16–30 weeks showed that exenatide BD lowered HbA1c by 0.8% from an average baseline of 8.1±0.6%[246].The impact of exenatide BD on HbA1c reductions was greater in patients with baseline HbA1c > 9%[241] and was maintained at 3 years[242] and only deteriorated modestly through 6 years (http://www.glycosmedia.com/library/Bydureon.pdf)[247, 248].

Liraglutide improved glycaemic control in RCTs when used as monotherapy or add-on therapy (Table 6)[241, 243, 249, 250]. Compared to glimepiride 8 mg/daily, liraglutide 1.2-1.8 mg/d monotherapy resulted in greater reductions in HbA1c (baseline HbA1c average 8.3%)(-0.6%, -0.9% and -1.1% for glimepiride, liraglutide 1.2 and liraglutide 1.8 respectively; treatment difference: -0.31, 95% CI: -0.54 to -0.08; p = 0.008 and -0.60, 95% CI: -0.83 to -0.38; p < 0.0001 for liraglutide 1.2 and 1.8mg respectively); and FPG (treatment difference −0.63, 95%CI : −1.17 to −0.09, p=0.02 and−0.99; 95% CI: −1.53 to −0.45, p < 0.001 for liraglutide 1.2 and 1.8 respectively) and PPG over 104 weeks[249]. In pooled patient data from 7 phase 3 RCTs from the liraglutide programme, 26 weeks of liraglutide 1.8 mg HbA1c reductions were lower in patients with baseline HbA1c ≤7.5% (0.7%) vs. baseline HbA1c >9.0% (1.8%)[251].

Lixisenatide significantly decreased HbA1c and PPG when used as mono- or add-on therapy[211-216, 252-259]. In a meta-analysis of RCTs Lixisenatide significantly reduced 2-h PPG from baseline (least square mean difference vs. placebo: -4.9 mmol/l, p < 0.001), glucose excursion (-4.5 mmol/l, p < 0.001) and postprandial glucagon (-19.0 ng/l, p < 0.001)[258]. Lixisenatide also reduced HbA1c and PPG but not FPG compared to placebo when added to basal insulin [259]

Exenatide QW (once-weekly) reduced HbA1c, FPG and PPG when used as mono- or add-on treatment [241, 243, 260, 261]. Exenatide once-weekly monotherapy was non inferior to metformin, superior to sitagliptin and similar to pioglitazone [241, 260]. When added to metformin, exenatide QW was more effective than adding either sitagliptin or pioglitazone[241, 261]. When added to metformin +/- sulfonylurea, exenatide QW resulted in similar HbA1c reductions to insulin glargine which were maintained at 3 years[223, 238, 241]. Similarly, when compared to once-daily or twice-daily insulin detemir exenatideQW resulted in greater HbA1c reductions over 26 weeks[241, 262].Extension of the DURATION-1 trial with patients converted to exenatide QW noted HbA1c and FPG were maintained over 5 years follow-up[263]. However, it must be noted that in this study 40% (105/258) did not complete the study which is a potential source of bias. Most of the loss of follow-up was due to withdrawal of consent and only 8 patients lost follow up because of “loss of glucose control”. The authors indicated that there were no differences in baseline characteristics between those who completed and did not

complete the study and the HbA1c reductions by 5 years were evident in the intent-to-treat analysis (-1.2%±0.1%) or the completers analysis (-1.6%±0.1%; baseline HbA1c 8.1%±0.9%).

Albiglutide improved glycaemic control when used as monotherapy or add-on therapy in phase 3 studies [252, 264, 265]. In a 104-week RCT, albiglutide provided a significantly greater reduction in HbA1c than placebo, sitagliptin and glimepiride when added to metformin, with similar results for FPG reductions[228]. When added to metformin and sulfonylurea, albiglutide did not meet the pre-specified non-inferiority margin of 0.3% when compared to pioglitazone over 52 weeks[225].

When added to metformin (with or without sulfonylurea), albiglutide resulted in similar HbA1c reductions compared to insulin glargine over 52 weeks [226]. As an add on to insulin glargine, albiglutide was non-inferior to insulin lispro at 26 weeks but did not meet the non-inferiority margins at 52 weeks[252, 266].

Dulaglutide 0.75mg and 1.5mg weekly were more effective than metformin and sitagliptin when used as mono- or as an add-on therapy to other oral glucose lowering treatments over 52 weeks[234, 236, 252].Dulaglutide 1.5 mg weekly was more effective and 0.75mg was non-inferior to insulin glargine when added to metformin and sulfonylureas over 52 weeks[239].

A meta-analysis of placebo controlled RCTs of at least 12 weeks in which information about ethnicity was available showed that the weighted mean difference of HbA1c with GLP-1 analogues was -1.16% (95% CI -1.48, -0.85 in the Asian-dominant studies (≥ 50% of study participants were Asian) and -0.83% (95% CI -0.97, -0.70) in the non-Asian-dominant studies (between-group difference -0.32% (95% CI -0.64, -0.01; p = 0.04))[267].

Impact on weight

GLP-1 RAs are associated with significant weight loss and reduction in waist circumstance but with much variation in individual responses and within-class differences (see the head-to-head section below) (**Table 7**)[252, 268-271]. When added to insulin, GLP-1 RAs resulted in significant mean weight loss of -3·22 kg (95%CI -4·90 to -1·54)[269].

Impact on BP

Several meta-analyses and RCTs showed that GLP-1 RAs resulted in a modest but significant systolic BP lowering effect (**Table 7**) [272-274]. This impact on BP was independent of baseline BP and the impact of GLP-1 RA on HbA1c or weight[272]. Reductions in diastolic BP were also observed with exenatide twice-daily (-1.08mmHg, 95% CI: -1.78 to -0.33)[273].

Others effects

GLP-1 RAs have modestly reduced total cholesterol, LDL and triglycerides with no improvements in HDL levels when compared to placebo or active comparators[275].

Safety and adverse events

GLP-1 RAs are generally well tolerated with nausea being the most common adverse event, which is usually transient resolving over 4-8 weeks and can be minimised by starting on a low dose followed by dose up-titration[28, 29, 241, 252]. The risk of hypoglycaemia in patients receiving GLP-1 RAs is low unless combined with insulin or sulfonylureas[28, 29, 241, 252]. Injection site reactions are common with some GLP-1 RAs such as exenatide QW and albiglutide (up to 17.6% for exenatide QW, up to 22% for albiglutide)[252]. The occurrence of antibodies is also common with GLP-1 RAs but these appear to be of little clinical significance and generally do not influence glycaemic control except very occasionally in patients with high titres who were receiving exenatide QW[29, 195, 241, 252].

The risk of pancreatitis and pancreatic cancer has attracted much attention but to date there is no definite causal link between GLP-1 RAs treatment and pancreatitis or indeed pancreatic cancer[276]. Several meta-analyses of randomised and non-randomised clinical trials and observational studies have shown no statistically significant increase of acute pancreatitis with GLP-1 RAs treatment in patients with T2DM[277-279]. In addition, the latest published cardiovascular safety trials did not show a significant increase in pancreatitis with GLP-1 RAs. The recommendation to avoid GLP-1 RA therapy in patients with a history of pancreatitis and discontinuation if pancreatitis develops is considered appropriate. Thyroid C- cell hyperplasia and medullary cell carcinoma were also raised as possible concerns in pre-clinical (rodent) studies; however clinical studies have not identified any significant problems [29, 241, 252].

Pre-clinical studies showed that GLP1 RAs have cardioprotective effects in heart failure and following myocardial ischaemia. GLP-1 RAs can have a favourable impact on many cardiovascular risk factors such as weight loss, lowering BP, improving endothelial function, reducing inflammation, lowering PAI-1, reducing postprandial lipaemia and modest reductions in LDL[66]. Several small studies in patients with and without diabetes showed a beneficial impact of GLP-1 RAs on left ventricular function in patients with heart failure and on myocardial function and the myocardial salvage index following ischaemia[66, 280]. However, GLP-1 RAs often increase resting heart rate (approx. 3 beats/minute), most likely by activating the GLP-1 receptor in the sinoatrial node [66]. RCTs using 24-hour ambulatory heart rate monitoring showed that dulaglutide 1.5 mg was associated with increased heart rate compared to placebo (least squares mean difference 2.8 bpm, 95%CI 1.5-4.2)[281], while dulaglutide 0.75mg and exenatide were not associated with increased heart rate compared to

placebo[281, 282]. Several large RCTs assessing the cardiovascular safety of liraglutide (LEADER), semaglutide (SUSTAIN 6), exenatide QW (EXSCEL) and dulaglutide (REWIND) are currently ongoing [66]. The lixisenatide (ELIXA) trial reported in 2015 showing no adverse cardiovascular outcomes in patients with T2DM and established CVD who were treated with lixisenatide, and no increase in heart rate[283].

Head-to-Head comparisons of GLP-1 RAs:

As several GLP-1 RAs are available with different chemical structures and formulations, the different pharmacokinetic and pharmacodynamic profiles seen in head-to-head trials may influence clinical decision making. A summary of the designs and results of the head-to-head trials can be found in **Tables 8 & 9**[206, 217, 220, 222, 232, 233, 240, 284-286]. Overall liraglutide 1.8mg and dulaglutide 1.5mg appear to have the greatest impact on HbA1c and liraglutide 1.8mg and exenatide QW the largest impact on weight reduction. Albiglutide seems to have less impact on HbA1c and weight reductions but was associated with less gastrointestinal side effects. Once-weekly preparations are more associated with injection site reactions than once or twice daily agents.

In general, longer-acting GLP-1 RAs show greater reductions in FPG but lesser impacts on PPG excursions than shorter-acting GLP-1 RAs[287, 288]. The differential impact on PPG is at least partly mediated by delayed gastric emptying, which is not subject to the tachyphylaxis with short-acting GLP-1 RAs, but can occur after treatment with long-acting GLP-1 RAs[287]. In addition, lixisenatide , in contrast to liraglutide, strongly suppresses post-prandial glucagon secretion[287]. Patient satisfaction was greater amongst those receiving exenatide QW or liraglutide than exenatide twice-daily[284].

GLP-1 RAs vs. Insulin

In a meta-analysis of RCTs that compared GLP-1 RAs vs. basal insulin progressively titrated to achieve FPG targets in patients with T2DM, GLP-1 RAs resulted in greater reductions in HbA1c (mean net change-0.14%, 95%CI -0.27, -0.02%; $p = 0.03$) and weight (-4.40 kg, -5.23, -3.56 kg; $p < 0.01$) while insulin caused greater reductions in FPG (1.18 mmol/l, 0.43, 1.93 mmol/l; $p < 0.01$)[289]. GLP-1 RAs were also associated with greater reductions in PPG compared to insulin[289]. Hypoglycaemia was reported less in the GLP-1 RA group (HR 0.45; 0.27, 0.76; $p < 0.01$) and GLP-1 RAs resulted in greater weight loss (−4.40 kg,95% CI−5.23, −3.56 kg; $p < 0.01$)[289]. Dulaglutide also resulted in greater reductions in HbA1c compared to insulin glargine when added to insulin lispro[290]

Insulin-GLP-1 RA combination

To simplify the co-administration of basal insulin and GLP-1 RAs, these two agents have been combined into a single injection, a fixed-ratio combination (IDegLira), which was launched in the UK

in 2014 [148]. IDegLira combines 50 units of insulin degludec with 1.8 mg of liraglutide[148]. The combination is titrated in the same way as insulin alone; thus, for every 1 unit of insulin injected, the individual also receives 0.036 mg liraglutide[148].

In a 26 week RCT of insulin-naïve patients HbA1c decreased by 1·9% ± 1·1% with IDegLira, compared with 1·4% ± 1·0% with insulin degludec, and 1·3% ± 1·1% with liraglutide[291]. The IDegLira group reported less nausea than the liraglutide group and less hypoglycaemia than the insulin degludec group[291]. These benefits were maintained at 52 weeks with HbA1c reductions of 1.84%, 1.40%, 1.21% for IDegLira, insulin degludec and liraglutide respectively[292]. IDegLira (5.7 mmol/l) and degludec (6.0 mmol/l) had similar FPG by study-end but liraglutide had higher FPG (7.3 mmol/l)[292]. The improvements in glycaemic control were achieved with 37% less daily insulin dose of IDegLira than insulin degludec[292]. IDegLira was associated with a significantly greater decrease in body weight (estimated treatment difference, -2.80 kg, $p < 0.0001$) and a 37% lower rate of hypoglycaemia compared with insulin degludec[292]. When used in patients who were already on basal insulin, HbA1C decreased by 1.9% with IDegLira vs. 0.9% in the insulin degludec group (treatment difference -1.1%; 95% CI -1.3, -0.8; $P < 0.0001$). Mean weight reduction with IDegLira was 2.7 kg vs. no weight change with degludec, and hypoglycemia incidence was comparable (24% for IDegLira vs. 25% for insulin degludec)[293].

Another fixed-ratio combination of lixisenatide and insulin glargine has completed phase 3 trials and has been submitted to the FDA (http://en.sanofi.com/NasdaQ_OMX/local/press_releases/sanofi_reports_positive_toplin_1951405_14-09-2015!07_00_00.aspx)[294]

SGLT-2 inhibitors

Currently available sodium-glucose co-transporter-2 (SGLT-2) inhibitors in Europe and North America are dapagliflozin, canagliflozin and empagliflozin. They can be used as monotherapy when diet and exercise are inadequate, and when metformin is not tolerated: they can also be used an add-on to other glucose-lowering agents including insulin[295]. Because their efficacy is dependent on the renal filtration of glucose, SGLT-2 inhibitors should not be initiated in patients with eGFR< 60 ml/min/1.73 m^2; however, in patients who are already on and tolerant of canagliflozin or empagliflozin these can be continued in patients with eGFR down to 45 ml/min/1.73 m^2[2296].

Mechanism of action

SGLTs are secondary active membrane symporters that transfer sodium down its concentration gradient, usually into the cell, in conjunction with the inward transfer of specific hexose sugars or

other specific molecules against their concentration gradient[297]. SGLTs in the intestine and kidneys transfer glucose across the luminal membrane into the enterocytes or ductal epithelial cells and glucose transporters (GLUTs) mediate passive transfer of glucose across basolateral membranes down its concentration gradient **(Figure 6)**[295, 298, 299].

The main SGLTs are SGLT-1 and SGLT-2 which are respectively responsible for intestinal glucose absorption and renal reabsorption of most of the filtered glucose[297, 300]. SGLT-2 is a low affinity high capacity glucose transporter in the S1 segment of the proximal tubules which is suited to reabsorption of a high concentration of filtered glucose entering the tubules, whereas SGLT-1 (high affinity low capacity glucose transporter) is suited to reabsorption of the remaining lower glucose concentration in subsequent segments[300-302].

Competitively inhibiting SGLT-2 can eliminate 60-90 g glucose/ day[303], but this amount can vary considerably according to renal function and the degree of hyperglycaemia[295]. The effects of SGLT-2 inhibition are self-limiting as the efficacy decreases as the hyperglycaemia lessens (and less glucose is filtered). The effects of SGLT-2 inhibition are insulin-independent and hence the efficacy is not altered by declining β-cell function or insulin resistance[29, 295]. However, the presence of insulin is still needed to service other physiological requirements as SGLT-2 inhibition does not treat the underlying endocrinopathies that contribute to the pathogenesis of T2DM, except by reducing the effects of glucotoxicity[29, 295]. SGLT-2 inhibition and the associated glucosuria result in mild diuresis and calorie loss enabling modest reductions in BP and weight[29, 295].However, the weight loss caused by SGLT-2 inhibitors is less than expected from the degree of glucosuria, with patients typically losing one quarter to one third of the weight loss predicted by their glycosuria. This is in part accounted for by an increase in calorie intake which correlated negatively with baseline BMI and positively with baseline eGFR [304]. Hence, The calorie reduction anticipated with a combination of an SGLT-2 inhibitor and a GLP-1 RA (which should counter increased calorie intake) would be expected to achieve significant weight loss; indeed in the 95 patients who were taking a GLP-1 RA in the CANVAS trial, addition of canagliflozin 300mg resulted in significant weight loss compared to placebo (least squares mean % change in weight difference -3.2%, 95% -4.5 to -2.0) over 18 weeks[305].

Pharmacokinetics

The pharmacokinetics of SGLT-2 inhibitors are summarised in **Table 10**[295, 306-310]. Empagliflozin is the most specific amongst the currently available SGLT-2 inhibitors. SGLT-2 inhibition by dapagliflozin (10 mg/d), canagliflozin (300mg/d) or empagliflozin (25mg/d) increases urinary glucose excretion similarly by 60-90 g/day[295, 311, 312]. Available SGLT-2 inhibitors are metabolised by uridine

diphosphate glucuronosyl transferases, thus avoiding interactions with drug metabolism through the P450 CYP pathways, and no significant drug interactions are reported[295, 313, 314].

Pharmacodynamics

Dapagliflozin: Compared to placebo, dapagliflozin 5-10mg / day in drug naive patients with T2DM reduced HbA1c by 0.8-0.9% with weight loss of 2.8-3.2 kg[315]. A meta-analysis of RCTs of 12-104 weeks duration showed that dapagliflozin (2.5-10 mg/d) improved HbA1c, FPG and weight compared to placebo when used as an add on therapy to metformin, insulin, TZDs, sulfonylureas or metformin±sitagliptin by (mean difference between groups (95%CI))−0.52% (−0.60, to −0.45), −1.52mmol/l (−1.75 to −1.29) and −1.61 kg (−1.97 to −1.26) respectively[316]. However, the usual clinical dose of 10mg dose showed somewhat greater efficacy[317].

The reductions in HbA1c and FPG were largely similar across different background treatments but largest when dapagliflozin was added to a sulfonylurea -0.96% (-0.86 to -0.52) and -1.47 mmol/l (-1.86 to -1.08)[316]. Changes in weight were similar regardless of the background treatment with the largest between group difference seen when dapagliflozin was added to insulin -2.45 kg (-2.99 to -1.92)[316]. Similar results were found when dapagliflozin was added to metformin and sulfonylureas[318].When compared to glipizide in a 52 weeks RCT with 156 weeks extension, dapagliflozin resulted in lesser HbA1c reductions in the initial 18 weeks of the trial but the coefficient of failure over 104 weeks was lower with dapagliflozin (0.13%/year) than with glipizide (0.59%/year) (differences of -0.46%/year, 95% CI -0.60,-0.33; p = 0.0001)[319]. HbA1c reductions were also greater in dapagliflozin by week-104 (-0.18%, 95% CI -0.33, -0.03; p = 0.021)[319]. Dapagliflozin also resulted in sustained weight loss (difference -5.1 kg, 95% CI: -5.7,-4.4) and a drop in systolic BP (difference -3.9 mmHg, 95% CI: -6.1,-1.7)[319].

Although the weight loss was modest, it was associated with significant improvements in health-related quality of life over 102 weeks[320]. Dapagliflozin also resulted in increased glucagon secretion from as early as 1 hour after administration, reaching a peak after 240 minutes[321].After 3 days of dapagliflozin treatment, the fasting plasma glucagon concentration was 32% higher than on day 1 while there was no change in the placebo group[321]. How this apparent compensatory mechanism operates is unestablished but SGLT-2 expression has recently been noted in pancreatic α-cells[322].

Canagliflozin: In a meta-analysis of RCTs, canagliflozin reduced HbA1c when used as monotherapy (weighted mean difference (WMD) -1.08%, 95% CI -1.25 to -0.90, p < 0.00001) or add-on treatment (-0.73%, 95%CI -0.84 to -0.61, p < 0.00001) compared to placebo[323]. When compared with active comparators, it reduced HbA1c by -0.21% (95%CI -0.33 to -0.08, p = 0.001)[323].HbA1c was also reduced with canagliflozin compared with sitagliptin (−0.24 %, 95 %CI −0.40 to −0.09, $p = 0.002$) and

glimepiride (−0.12 %, 0.95 %CI −0.23 to −0.01, $p = 0.03$)[323], FPG was reduced compared to placebo (−33.50 mg/dl, 95 %CI −39.22 to −27.78, $p < 0.00001$) and active comparators (−15.86 mg/dl, 95 %CI −23.17 to −8.56, $p < 0.00001$)[323]. Canagliflozin resulted in greater weight loss compared to placebo (-2.81 kg, 95%CI -3.26 to -2.37) and active comparators (-3.49 kg, 95%CI -4.86 to -2.12)[323], particularly when compared to glimepiride (−5.40 kg, 95 %CI −5.95 to −4.85, $p < 0.00001$)[323].

When added to insulin treatment (mostly basal-bolus regimen) canagliflozin 100 and 300 mg resulted in significant reductions in HbA1c compared to placebo from a baseline of 8.3% (-0.62% (95% CI -0.69 to -0.54; p < 0.001) and -0.73% (95% CI -0.81 to -0.65); p < 0.001 for 100mg and 300mg respectively) at 18 weeks which were sustained up to 52 weeks[324]. Reductions in FPG and weight were as expected and with greater incidence of hypoglycaemia, genital infections and hypovolaemia[324]. Canagliflozin 300mg administered immediately before a mixed meal tolerance test reduced PPG in a small RCT without causing any further increases in urinary glucose excretion which might suggest other mechanisms such as SGLT-1 inhibition in the gut[325]. Similar to dapagliflozin, the glycaemic lowering and weight loss effects of canagliflozin were more durable than those achieved with sulfonylureas up to 104 weeks[326].

Canagliflozin caused reductions in systolic and diastolic BP when compared to placebo or active comparators (vs. placebo: systolic BP (−5.05mm Hg, 95 %CI −6.81 to −3.28, $p < 0.00001$), diastolic BP (−2.43, 95 %CI −3.29 to −1.57, $p < 0.0001$); vs. active comparator: systolic BP (−4.34 mmHg, 95 %CI −5.31 to −3.36, $p < 0.00001$); diastolic BP(−2.17, 95 %CI −2.79 to −1.54, $p < 0.00001$)[323].

Empagliflozin: In 24-week randomised placebo controlled trials, empagliflozin resulted in HbA1c, weight and systolic BP reductions of 0.7%-0.8%, 1.5-2.5kg and 2.9-4.1 mmHg respectively, which were significant compared to placebo when used as monotherapy or when added to metformin, metformin+sulfonylurea or pioglitazone ± metformin[327-330]. The reductions in HbA1c and weight were maintained in trial extensions up to 76 weeks[331-334].

When compared to sitagliptin as monotherapy, empagliflozin resulted in similar HbA1c reductions to sitagliptin but greater reductions in FPG, weight and systolic blood pressure[327]. Over 104 weeks, empagliflozin was non-inferior to glimepiride when added to metformin treatment with much less hypoglycaemia in the empagliflozin group[335].

When added to basal insulin, with or without metformin ± sulfonylurea, empagliflozin resulted in an HbA1c reduction of 2.0-2.5% compared to placebo over 78 weeks. In addition, there was 2.4-4.1kg weight loss[336]. When added to a multiple daily injection (MDI) insulin regimen HbA1c dropped by -0.81 ± 0.08%, -1.18 ± 0.08% and -1.27 ± 0.08% with placebo, empagliflozin 10 mg,

and empagliflozin 25 mg, respectively after 52 weeks treatment[337]. Empagliflozin treatment also reduced insulin doses (-9 to -11 international units/day) and weight (-2.4 to -2.5 kg) without increasing the risk of hypoglycaemia compared to placebo[337].

In a 12-week RCT of patients with T2DM and systolic and diastolic BP of 130-159 and 80-99 mmHg respectively, the adjusted mean differences vs. placebo in change from baseline in mean 24-h systolic BP was -4.16 mmHg (-5.50, -2.83) and diastolic BP with 25 mg of empagliflozin. -1.72 mmHg (95% CI -2.51, -0.93) with 25 mg empagliflozin (both P < 0.001)[338].

Compared to placebo, empagliflozin resulted in adjusted mean HbA1c difference of −0·68% (–0·88 to −0·49) in patients with eGFR 60-90 and −0·42% (–0·56 to −0·28) in patients with eGFR 30-60 over 24 weeks and the treatment was well tolerated[339].

Single and chronic administration of empagliflozin resulted in an increased glucagon response to a mixed meal[340].

Safety and adverse events

SGLT-2 inhibitors are associated with low risk of hypoglycaemia except when used in combination with insulin or sulfonylureas[295].The low risk of hypoglycaemia reflects the ability of remaining SGLT-2 (and SGLT-1) to reabsorb all of a lesser filtered glucose load as the blood glucose level declines, emphasising the self-limiting nature of this mode of action[295]. Compared to glipizide, dapagliflozin resulted in significantly lower risk of hypoglycaemia (4.2 vs. 45.8%)[319]. Canagliflozin treatment was associated with similar rates of hypoglycaemia compared to placebo when used as monotherapy or as an add-on therapy except when added to sulfonylurea (RR 1.49, 95 %CI 1.14 to 1.95, $p = 0.004$)[323]. The percentage of patients having confirmed hypoglycaemic events with empagliflozin treatment was< 1% when used as monotherapy, and 1.4-2.4% when used as add-on to metformin or pioglitazone, but increased to 11.5-16.1% when combined with sulfonylureas and the percentage increased to 35-58% when added to insulin[29, 241, 313]

SGLT-2 inhibitors are associated with increased risk of genital infections but an increase in urinary tract infection (UTI) has not been consistently reported[295]. Compared to sulfonylureas, dapagliflozin was associated with increased risk of genital and urinary tract infections (dapagliflozin: 14.8 and 13.5%, respectively; glipizide: 2.9 and 9.1%, respectively)[319]. There was no increased risk of UTIs in canagliflozin treated patients but there was increased risk of genital tract infections (vs. placebo, RR 3.76, 95 %CI 2.23 to 6.35, $p < 0.00001$; vs. active comparators, RR 4.95, 95 %CI 3.25 to 7.52, $p < 0.00001$) more in women than men but none of the reported infections was severe and all were resolved with simple treatment[323]. In a pooled analysis of RCTs, genital mycotic infection occurred more commonly with canagliflozin 100 and 300 mg compared to placebo in women (10.4%,

11.4%, 3.2%) and men (4.2%, 3.7%, 0.6%). Similar results were found when canagliflozin was compared to active control (females: 14.7%, 13.9%, 3.1%; males: 7.3%, 9.3%, 1.6%)[341]. The infections were generally mild and easy to treat but there was lack of laboratory confirmation for most events[341]. Similarly, empagliflozin was associated with UTI in some trials but not others while all trials showed increased risk of genital infections[313].

SGLT-2 inhibitors are also associated with small increases in LDL but also corresponding increases in HDL: these effects may be slightly greater with canagliflozin [323, 342].There is inconsistency regarding the risk of osmotic diuresis and hypovolaemia[295, 343]. The risks of osmotic diuresis-related adverse events (AEs) were higher with canagliflozin compared to placebo(RR 3.93, 95% CI 2.25 to 6.86, $p < 0.00001$) or active comparators (RR 2.57, 95 %CI 1.26 to 5.25, $p = 0.009$), while volume-related AEs were similar compared to placebo or active comparators[323]. In a 12-week RCT canagliflozin 300mg vs. placebo resulted in increased urinary volume and decreased plasma volume at week 1 (-5.4% vs.4.3%, p=0.02) both of which were attenuated by week 12[344]. In a pooled analysis of data from >11,000 patients with T2DM, empagliflozin was not associated with an increased frequency of volume depletion-related events, but there was a higher frequency of such events in patients ≥75 years of age receiving empagliflozin 25 mg and in patients taking loop diuretics receiving empagliflozin 10 mg[345].

There is possibly an increased risk of fractures with SGLT-2 inhibitors, particularly with canagliflozin. A RCT with dapagliflozin had no effect on markers of bone formation or resorption or bone mineral density after 50 weeks of treatment in men and post-menopausal women with T2DM inadequately controlled on metformin[343, 346]. However, canagliflozin was associated with increased urinary calcium and is associated with modest increases in phosphate, possibly secondary to tubular re-absorption, and parathyroid hormone and reductions in 1,25 dihydroxy-vitamin D[347]; The FDA required a follow-up of upper limb fractures of patients on canagliflozin after an adverse imbalance in cases was reported in short-term trials[37]. In a RCT, consisting of a 26-week, double-blind, placebo-controlled period and a 78-week, double-blind, placebo-controlled extension that included 716 patients with T2DM aged 55-80 years, canagliflozin treatment was associated with a decrease in total hip bone mass density (measured using DEXA) over 104 weeks, (placebo-subtracted changes: -0.9% and -1.2%, for 100mg and 300mg respectively), but not at other sites measured[348].In addition, in a pooled analysis from 9 placebo- and active-controlled studies (N = 10,194) of canagliflozin the incidence of fractures was similar with canagliflozin (1.7%) vs. non-canagliflozin (1.5%) in the pooled analysis that excluded the CANVAS study (HR 1.09, 95%CI 0.71–1.66 for all canagliflozin)[349]. However, in CANVAS, there was a significant increase in fractures with canagliflozin (4.0%) vs placebo (2.6%) (HR 1.51, 95%CI 1.04–2.19 for all canagliflozin patients) as well as increased fall-

related adverse events in the canagliflozin group. But CANVAS patients, were older, with a high risk of cardiovascular disease, and with lower baseline eGFR and higher diuretic use[349].

Several cases of euglycaemic and hyperglycaemic diabetic ketoacidosis (DKA) have been reported in patients who received SGLT-2 inhibitors[350-353]. More recently it was reported that the DKA prevalence in 17,596 patients from randomized studies of canagliflozin was 0.07% (n=12)[353]. Causality has not been proven, but many of these cases were in insulin-treated T2DM patients who had reduced or stopped insulin or experienced an intercurrent illness that would increase the demand for glucose or during starvation[354]. A lack of insulin allows increased lipolysis and conversion of excess fatty acids to ketones, but the hyperglycaemia is typically mild, presumably because the SGLT-2 inhibitors are reducing the blood glucose[350, 351, 354]. In addition, many cases turned out to have Latent Autoimmune Diabetes of Adults (LADA): essentially the reduction of insulin dose by the patient had revealed a Type 1 Diabetes, Other cases resulted from off-label use of SGLT-2 inhibitors in patients with Type 1 Diabetes[350, 351, 354]. Thus it is important that insulin-treated patients undertaking self-monitoring of blood glucose should not discontinue insulin when they observe a reduction in blood glucose after introduction of an SGLT-2 inhibitor. The SGLT-2 therapy is to improve glycaemic control but not to obviate the need for insulin.

Pooled analysis of dapagliflozin phase 2/3 trials suggests a possible beneficial impact of dapagliflozin on cardiovascular disease[66]. Several RCTs are assessing the cardiovascular outcomes in patients treated with SGLT-2 inhibitors including: EMPA-REG (Empagliflozin), CANVAS (Canagliflozin), DECLARE (Dapagliflozin) and NCT01986881 (Ertugliflozin). The EMPA-REG OUTCOME study recently showed that in patients with T2DM and cardiovascular disease empagliflozin lowered a composite end-point of non-fatal myocardial infarction, non-fatal stroke and death from cardiovascular causes when added to standard therapy in comparison to placebo (HR0.86; 95.02% CI, 0.74 to 0.99; P=0.04 for superiority)[355]. Empagliflozin treatment also lowered the risk of cardiovascular death (HR 0.62; 95% CI, 0.49 to 0.77; P<0.001), death from any cause (0.68; 95% CI, 0.57 to 0.82, P<0.001) and hospitalisation from heart failure (0.65; 95% CI, 0.50 to 0.85; P=0.002) [355]. Subgroup analyses showed that there was heterogeneity for the primary outcome; the benefits of empagliflozin were more evident in Asians, patients with BMI < 30 kg/m^2, HbA1c <8.5%, those not on insulin treatment, and those with nephropathy[355]. The impact of empagliflozin on death from cardiovascular causes was consistent across all subgroups[355]. Results of other cardiovascular outcome trials with dapagliflozin and canagliflozin are awaited with interest.

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Other agents

Dopamine D2 receptor agonists

Bromocriptine quick release (QR) (Cycloset) is an ergot alkaloid dopamine D_2 receptor agonist that is licensed in some countries outside of Europe for the treatment of T2DM as an adjunct to lifestyle changes[356, 357]. The impact of bromocriptine on glycaemic parameters has been noted since 1980 [358]. The drug provides a morning boost to hypothalamic dopamine, consistent with normal diurnal glucoregulation. This assists a reduction of sympathetic tone, neural suppression of hepatic glucose production, and improved peripheral glucose disposal without affecting insulin levels[29, 356, 358, 359]. In a recent meta-analysis bromocriptine-QR add-on therapy lowered HbA1c compared with placebo (- 6.52 mmol/mol; 95% CI, - 8.07 to - 4.97 mmol/mol) and FPG(-1.04 mmol/l; 95% CI-1.49 to-0.59 mmol/l) but had no effect on PPG [360].Bromocriptine QR was weight neutral and had no increased risk of hypoglycaemia, hypotension, or cardiovascular effects[360]. However, Bromocriptine-QR had more gastro-intestinal side effects of nausea and vomiting[360]. In a large RCT (3,095 patients) bromocriptine QR (as monotherapy or add on to glucose lowering agents including insulin) was shown to reduce the risk of cardiovascular disease compared to placebo (HR 0.60 (95% CI 0.35–0.96)) by 52 weeks[361].

Bile acid sequestrants

Bile acid sequestrants are established treatments for dyslipidaemia and reduce the risk of cardiovascular disease [362]. In 2008, the FDA licensed colesevelam as an adjunct to lifestyle to improve glycaemic control in T2DM [363]. The mechanism may involve the passage of bile acids more distally along the intestine, possibly activating bile acid receptors on L-cells and increasing GLP-1 secretion. Reduced return of bile acids to the liver may also affect glucose metabolism via reduced activation of hepatic farnesoid receptors[29]. Colesevelam reduced HbA1c by 0.30-0.54% when used in combination with metformin, sulfonylureas, pioglitazone or insulin, with no increased risk of hypoglycaemia or weight gain[362, 364]. Despite its favourable impact on LDL and HDL cholesterol levels, colesevelam increased triglycerides by 11-22%[362].

Pramlintide

Pramlintide is a soluble analogue of islet amyloid polypeptide (IAPP), introduced in 2005 as an injectable meal-time adjunct to a basal-bolus insulin regimen[365]. It assists glycaemic control and weight control through a centrally-mediated effect via the area postrema which activates neural pathways that enhance satiety, suppress pancreatic glucagon secretion and slow gastric emptying[365]. Modest reductions in HbA1c, typically 0.3-0.6% have been reported in trials, alongside body weight

reductions of 1-2 kg and reductions of the bolus insulin requirement[365]. Use of pramlintide adds to the burden of mealtime injections and requires care with dose adjustments to minimise risk of nausea and hypoglycaemia[365].

Treatment algorithm

The treatment options for patients with T2DM now extend to a variety of drug classes with different mechanisms of actions, lower risk of hypoglycaemia and favourable impact on weight. Also, the availability of several agents within most classes offers choice with regard to pharmacokinetics, pharmacodynamics and the timing and mode of delivery. However, it is often difficult to make direct comparisons when long-term head-to-head studies are not available, and it is difficult to determine suitability on an individualised patient basis without studies in particular patient sub-groups. Overall, the choice of any treatment must balance efficacy with safety, tolerability with adherence, budgets with resources, and practical issues around realistic targets, monitoring, and life situations[37].

Metformin is firmly established as preferred first line pharmacotherapy in patients with T2DM[37]; The results of the EMPA-REG OUTCOME study raise expectations for the SGLT-2 inhibitors and results of similar trials with other members of the class will help to determine the positioning of this class in the treatment algorithm. It must be noted that the choice of metformin as first-line therapy is mainly based on the UKPDS which included 342 patients assigned to metformin while the EMPA-REG included 4,687 empagliflozin-treated patients. On the other hand, the study population of EMPA-REG included patients with advanced disease and high cardiovascular disease risk while the UKPDS population was that of newly diagnosed T2DM. If HbA1c targets are not met with metformin treatment within 3 months it is recommended to add another differently-acting agent[37]. Whilst the various oral agents will often have similar efficacy, the injectables (GLP-1 RAs and insulin) may offer greater HbA1c lowering[243]. It is important, however, to appreciate that efficacy is not just about HbA1c but must always take into account a "package" of effects that includes risk of hypoglycaemia, weight gain, general tolerability and long-term safety. For example, the risk of weight gain and hypoglycaemia is higher with sulfonylureas and insulin, while DPP-4 inhibitors and SGLT-2 inhibitors have a more favourable impact on weight and low risk of hypoglycaemia[37]. TZDs have a low risk for hypoglycaemia but increase weight and risk for heart failure and bone fractures[37]. The importance of an individualised approach to treatment, based on patients' circumstances and needs is emphasised with regard to the selection of agents for people who drive, the elderly, frail and those with renal, neural and other co-morbidities that restrict therapeutic choice.

If adding a second agent fails to achieve or maintain acceptable control , then adding a third differently-acting agent may be indicated[37]. Most classes of agents can be combined with additive

efficacy, although addition of DPP-4 inhibitors is unlikely to offer meaningful extra control in combination with GLP-1 RAs. If triple combinations are inadequate then introduction of insulin(usually basal initially with continued metformin) is needed; if this is insufficient then the addition of meal time insulin or a GLP-1 RA may be considered, or possibly an SGLT-2 inhibitor[37]. The addition of a GLP-1 RA in this context might be a useful treatment strategy as this carries less risk of hypoglycaemia compared to adding meal time insulin and has a better impact on weight.

The availability of increasing numbers of agents that are given less than daily might be attractive for many patients and might enhance compliance. The outcomes of ongoing cardiovascular safety studies may clarify the T2DM treatment algorithm further. Indeed further long-acting GLP-1 RAs, DPP-4 inhibitors and SGLT-2 inhibitors are in development[366-370] as reviewed previously[19, 27].

Lessons for future therapies

Better understanding of the pathogenesis of T2DMhas informed the development of newer classes of treatments and novel compounds in development[371]. However, treatments that have longer lasting metabolic impacts and that are able to improve or prevent the continuing decline in β-cell function are needed. Clearly, safety is of paramount importance. The adverse effects that emerged during the use of several agents that have been discontinued have highlighted the importance of maintaining pharmacovigilance while improving the metabolic deficits. Minimising hypoglycaemia, weight gain, and cardiovascular events while avoiding any increased risk of cancer are crucial for any new treatments particularly since such treatments may need to be taken for many years. In addition, in real life the trial medications will be used in a more varied population and the drugs might be prescribed by less specialised professionals to patients who will not receive the intensive follow up and monitoring of RCTs[372]. This is highlighted by the protracted usage required for some safety signals (e.g. CV events) to emerge[372].

When considering safety it can be extremely difficult to interpret signals from pre-clinical studies or indeed have available the most appropriate models to decide which treatments should be developed further. Another challenge is to identify and interpret adverse signals in clinical trials and then extrapolate these to real-life[372]. Faint signals from pre-registration trials can take a decade or more to reveal their clinical importance and are often confounded by several biases including treatment allocation and detection of complications. While there is increasing pressure to ensure safety, the regulatory agencies have a difficult task to strike a balance between being over cautious and making sure that newer beneficial treatments are made available in a safe but timely manner[372].

In addition, better understanding of the factors that might be responsible for the variations in responses of individuals to a particular treatment and the impact of pharmacogenetics on pharmacokinetics and efficacy will allow more personalised and patient-centred future therapies[30].

Summary and conclusion

Many different glucose-lowering therapies are now available to address different aspects of the pathogenesis of T2DM through a range of actions that vary in efficacy, convenience, adverse events profile and cost. The potential "value" of a therapy is much more than cost-benefit, as it is based on a "package" of attributes that takes account of long-term safety, tolerability, risk of hypoglycaemia and weight gain, and suitability in the face of comorbidities and other medications. Individualised therapy also requires tailoring to patient needs and preferences based on an adequate appreciation of the patient's circumstances, understanding and commitment.

Newer agents (such as DPP-4 inhibitors, GLP-1 RAs and SGLT-2 inhibitors) have low risk of hypoglycaemia (except when combined with insulin or sulfonylurea) and are associated with either weight loss or weight neutrality, but they are more expensive than older agents (such as sulfonylureas or meglitinides). Recent studies have provided encouraging information about the safety profiles of many of these newer agents and supported their value in the challenge to provide early, effective and sustained glycaemic control in T2DM. While metformin remains the preferred initial pharmacotherapy (albeit that some patients do not tolerate it), an individualised approach is required to assess treatment targets and to achieve these in the safest possible manner.

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Table 1. Summary of currently available glucose lowering treatments in patients with T2DM. Adapted from Bailey 2015, and ADA-EASD guidelines References 29 and 37

Class (Year Introduced) Examples	Dosing	MOA	Physiological impact	Glucose lowering efficacy	Advantages / Disadvantages	CV Safety	Cost
Sulfonylureas (1956) Gliclazide* Glipizide Glimepiride Glyburide (glibenclamide)	OD, BD	– Increases insulin secretion by binding to SUR-1 on β-cells, resulting in closure of the K^+ATP channels and calcium influx and depolarization	Increase insulin secretion	High	Advantages – Oral – Long-term safety Disadvantages – Hypoglycaemia – Weight gain – Need for SMBG – Dose titration	Conflicting results from database studies, but no adverse outcomes from more recent interventional studies	Low
Biguanide (1957) Metformin Metformin SR	OD, BD	– AMPK activation – Improve cellular insulin signaling – Reduce respiratory chain activity – Alters gut glucose/ lactate metabolism	Reduce hepatic glucose output Improve insulin sensitivity Increase GLP-1 levels	High	Advantages – Long-term safety – Weight neutral – Low risk of hypoglycaemia Disadvantages – GI side effects – Multiple possible contraindictions especially renal impairment	Reduction in CV disease	Low
AGI (1995) Acarbose Miglitol Voglibose	Up to TDS with meals	– Inhibit α-glucosidase in the gut	Slow intestinal carbohydrate digestion, which delays absorption	Modest	Advantages – Weight neutral Disadvantages – GI side effects	Unknown, preliminary evidence of benefits	Moderate
Meglitinides (1997) Nateglinide Repaglinide	With meals	– Binds to SUR-1 on β-cells, but at a different site to SU, resulting in a more rapid and shorter action than SUs	Increase insulin secretion	Intermediate to high	Advantages – Rapid short-acting – Suitable for prandial use Disadvantages – Weight gain – Hypoglycaemia – Need for SMBG (but less than SU)	CVD not adversely affected in the NAVIGATOR trial	Moderate

Class (Year Introduced) Examples	Dosing	MOA	Physiological impact	Glucose lowering efficacy	Advantages / Disadvantages	CV Safety	Cost
TZDs (1997) Pioglitazone Rosiglitazone**	OD	– PPAR-γ agonists	Increase insulin sensitivity Reduce FFA release	High	Advantages – Low risk of hypoglycaemia – May reduce blood pressure – Possible effect on NASH Disadvantages – Unresolved long-term safety – Fractures – Weight gain – Oedema and heart failure	– Oedema and increased risk of heart failure – Debated impact on CVD – Pioglitazone reduced composite endpoint of all-cause mortality, nonfatal myocardial infarction, and stroke in the PROactive trial	Low
DPP-4 inhibitors (2006) Sitagliptin Vildagliptin* Saxaglitpin Linagliptin Alogliptin	OD, BD	– Inhibit DPP-4 activity which increases endogenous incretin levels	Glucose-dependent increase in insulin secretion Glucose dependent inhibition of glucagon secretion	Intermediate	Advantages – Weight neutral – Low risk of hypoglycaemia (unless combined with SU) – Possible benefit on β-cell survival Disadvantages – Unknown long-term safety – Increased risk of pancreatitis – Possible increased risk of liver dysfunction with vildagliptin	– No increase CVD risk in RCTs except increased hospitalization with heart failure with saxagliptin. More RCTs to report in near future	High

Class (Year Introduced) Examples	Dosing	MOA	Physiological impact	Glucose lowering efficacy	Advantages / Disadvantages	CV Safety	Cost
SGLT2 inhibitors (2012) Canagliflozin Dapagliflozin Empagliflozin	OD	– Inhibit SGLT-2 transporters in proximal renal tubules	Increase urinary glucose excretion	Intermediate to high	Advantages – Weight loss – Blood pressure reduction – Low risk of hypoglycaemia (unless combined with insulin or SU) – Possible sustained HbA1c reductions Disadvantages – Unknown long-term safety – Association with genital and possibly urinary tract infections – Osmotic diuresis, possible risk of hypotension and falls – Possible increased risk of fractures – Small increased risk of DKA	– Empagliflozin reduced CVD in RCT – More RCTs will report in near future.	High
Dopamine-2 agonist (2009) Bromocriptine QR	OD	– Activate hypothalamic dopamine receptors	Modulates hypothalamic regulation of metabolism via neural hepatic glucose output Increase glucose disposal	Modest	Advantages – Weight neutral – Low risk of hypoglycemia Disadvantages – Dizziness – Nausea – Fatigue	– Reduce CVD risk	High
Bile acid sequestrant (2008) Colesevelam	OD, BD	– Increase hepatic bile salts production – Increased GLP-1 secretion – Activation of liver farnesoid receptors	? Reduce hepatic glucose output ? Increase incretin secretion	Modest	Advantages: – Low risk of hypoglycaemia – Lower LDL – Weight neutral – Increase HDL Disadvantages – Constipation – Increase triglycerides – Could affect absorption of some drugs	– Reduce the risk of CVD (licensed as cholesterol lowering treatment)	High

Class (Year Introduced) Examples	Dosing	MOA	Physiological impact	Glucose lowering efficacy	Advantages / Disadvantages	CV Safety	Cost
Insulin (1920s) Rapid-acting Aspart Lispro Glulisine Short-acting Humulin-S Insuman rapid Intermediate-acting Insulatard Humulin-I Insuman basal Long-acting Glargine Detemir Degludec Biphasic pre-mixed	OD to QDS	– Directly activates the insulin receptor	Increase glucose disposal Reduce hepatic glucose output Decrease lipolysis	High	Advantages – Injectable – More sustained glycemic improvements compared with other agents Disadvantages – Weight gain – Hypoglycemia – Need for SMBG – Fluid retention	– Ongoing debate, but RCTs have not shown increased risk	Variable
GLP-1 RAs (2005) Exenatide Liraglutide Lixisenatide Albiglutide Dulaglutide	OD, BD, QW	– Activate the GLP-1 receptor	Glucose-dependent increase in insulin secretion Glucose dependent inhibition of glucagon secretion Reduce post-prandial glucose excretion Increase satiety Weight loss	High	Advantages – Weight loss – Low risk of hypoglycemia (unless combined with SU) – Possible impact on β-cell survival/sustained HbA1c reductions Disadvantages – injectable – GI side effects – Unknown long-term safety – Unconfirmed increased risk of pancreatitis	– Possible beneficial impact from non-randomised studies – Lixisenatide did not alter CV disease in RCT – More RCTs will report soon	High

Class (Year Introduced) Examples	Dosing	MOA	Physiological impact	Glucose lowering efficacy	Advantages / Disadvantages	CV Safety	Cost
Amylin analogue (2005) Pramlintide *	TDS	– Synthetic soluble analogue of human amylin	Reduce glucagon secretion Increase satiety Slow gastric emptying	Modest	Advantages – Weight loss – Reduced insulin dose Disadvantages – Injectable – Unknown long-term safety – Increased risk of hypoglycaemia, (careful patient selection and instruction, and insulin dose adjustments required) – Only used with mealtime insulin	– Unknown	High

AGI: α- glucosidase inhibitors; AMPK: adenosine 5′-monophosphate activated protein kinase; CV, cardiovascular; DKA: Diabetic Ketoacidosis; DPP-4, dipeptidyl peptidase-4; FFA, free fatty acid; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; IGT, impaired glucose tolerance; MOA, mechanism of action; NASH: non-alcoholic steatohepatitis; PPAR-γ, peroxisome proliferator-activated receptor-γ; RCT, randomized control trial; SGLT2, sodium-glucose co-transporter 2; SMBG, self-monitored blood glucose; SU, sulfonylurea; SUR-1, sulfonylurea receptor-1; TZD, thiazolidinedione. Not all agents have an indication for the treatment of type 2 diabetes in all regions. * not available in all regions; ** Discontinued in Europe.

Table 2: Sulfonylurea pharmacokinetics. Adapted from Bailey and Krentz, in Textbook of Diabetes 6th edition in press, 2016. Wiley. *Chlorpropamide is no longer used in many regions

Agent	Dose range (mg/day)	Duration of action (h)	Metabolites	Elimination
Tolbutamide	500–2000	6–10	Inactive	Urine 100%
Glipizide	2.5–20	6–16	Inactive	Urine ~70%
Gliclazide	40–320	12–20	Inactive	Urine ~65%
Gliclazide MR	30–120	18–24	Inactive	Urine ~65%
Glimepiride	1.0–6.0	12–>24	Active	Urine ~60%
Glibenclamide (glyburide)	1.25–15	12–>24	Active	Bile >50%
Chlorpropamide*	100–500	24–50	Active	Urine >90%

Table 3: Tissue specific effects of PPAR-γ activation. CPT, carnitine palmitoyl transferase; CRP, C-reactive protein; FATP1, fatty acid transport protein-1; GLUT-4, insulin-sensitive glucose transporter -4, HSD-1, hydroxysteroid dehydrogenase type 1; LPL: lipoprotein lipase; IRS, insulin-receptor substrate, ABCA1, ATP-binding cassette A1; SR, scavenger receptor; iNOS, inducible nitric oxide synthase; MMP-9, matrix metalloproteinase 9; MCP-1, monocyte chemoattractant protein 1; PDK-4, pyruvate dehydrogenase kinase 4; PI3K, phosphatidyl inositol 3-kinase

Adipose tissue	Skeletal muscle	Liver	Vascular endothelium
Adipocyte differentiation	Glucose uptake (increased GLUT4, increased PI3K, decreased PDK-4)	Decreased inflammation (decreased CRP)	Decreased intercellular adhesion molecules
Fatty acid uptake and storage (increased FATP1, increased acyl-CoA synthase)			Decreased endothelin
Increased adiponectin			Cholesterol efflux (increased ABCA-1 and SR-B1)
Decreased 11βHSD-1			Decreased iNOS
Lipolysis (Increased lipoprotein lipase)			Decreased interleukin-6, MMP-9 and MCP-1
Glucose uptake (increased IRS-1, IRS-2, PI3K, GLUT-4, Cbl-associated protein, and glycerol kinase)			

DELETE

Table 4: Summary of the pharmacokinetic properties of currently available DPP-4 inhibitors.

Agent	t1/2 (hours)	Elimination	Metabolite	% inhibition of DPP-4 activity	DPP-4 selectivity*
Sitagliptin	~12.4	~87% renal ~13% faeces	Almost all eliminated unchanged	Doses > 50 mg/d >80% inhibition	>2600 vs DPP-8; >5500 vs DPP-9
Vildagliptin	~3	~85% renal ~15% faeces	Inactive metabolites	50 mg dose, > 90% inhibition per 12 hours	~270 vs DPP-8; ~32 vs DPP-9
Saxagliptin	~2.5 (~3.1 for metabolites)	~75% renal (includes metabolites) ~22% faeces	Active main metabolite	Single dose > 2.5 mg 50-79% inhibition	~390 vs DPP-8; ~77 vs DPP-9
Linagliptin	~12	~5% renal >80% faeces	Minimal metabolism	Single dose 5 mg >70% inhibition	~40,000 vs DPP-8; >10,000 vs DPP-9
Alogliptin	~21	~76% renal ~13% faeces	mostly excreted unchanged	Single dose 25 mg >75% inhibition	>14,000 vs DPP-8; >14,000 vs DPP-9
Omariglitpin	~63 (steady-state after 2–3 weeks)	Mainly renal	Minimal metabolism	24 hour post-dose > 95%	>41,000 vs DPP-8; >41,000 vs DPP-9
Trelagliptin	54	Mainly renal	Minimal (hepatic, via CYP 2D6)	77%	?

* Fold difference in affinity for DPP-4 vs other dipeptidyl peptidases based on data presented by Deacon (*Diabetes, Obesity and Metabolism* 13: 7–18, 2011)

Table 5: Summary of the pharmacokinetic properties of available GLP-1 RAs.

Drug	**Structure** Sequence homology	**IC_{50}** nM	**Dose**	**Admin**	**Cmax**	**Tmax**	**T1/2**	**Elimination**
Exenatide twice-daily	Exendin-4 53%	0.55	5,10 ug	BD	~160-250 pg/ml	2-3h	~3.5h	Renal
Liraglutide	GLP-1 97%	0.11	0.6, 1.2, 1.8	OD	Steady state ~34	10-14h	11.6-13h	Peptidases in blood

			mg		nmol/L (1.8 mg dose)			
Exenatide once weekly	Exendin-4 53%	0.55	2mg	QW	Steady state ~300 pg/mL	2-6 wks at steady state	Unspecified	Renal (~10 wks to fully clear)
Lixisenatide	Exendin-4 plus extra Lys residues	1.4	20ug	OD	~190	1.2-2.5h	2-4h	Renal
Albiglutide	GLP-1 97%	?	30, 50 ug	QW	4.4 ug/mL (50ug dose)	3-5 days	~5 days	Peptidases
Dulaglutide	GLP-1 91%	?	0.75. 1.5 mg	QW	114 ng/mL (1.5mg dose)	2-4 wks at steady state	~4.7 days	Peptidases

Table 6: Summary of the impact of GLP-1 RAs on glycaemic parameters. HbA1c change is in % and plasma or blood glucose levels in mmol/l unless stated otherwise. Data presented as averages or mean (95% CI) from multiple studies when available. FPG: Fasting plasma glucose; FBG: Fasting Blood Glucose; PPG: Post-Prandial Glucose; A1c: HbA1c. ↓, decrease. Based on Refs 203-267

	Monotherapy	Add-on to oral agents	Add-on to basal insulin	Meta-analysis
Exenatide twice-daily	↓A1c 0.7–0.9 ↓FBG 0.97-1.03 ↓PPG 1.18-1.37	↓A1c 0.4–0.9 ↓FBG 0.3–1.6	↓A1c 1-2 ↓FBG 1.6	↓A1c 1.1 (-1.22 to -0.99) ↓FPG 1.16 (-1.35 to -0.97)
Liraglutide 1.2-1.8mg	↓A1c 0.6-0.90 ↓FPG 0.52-2.5 ↓PPG 1.7−2.1	↓A1c 1.0-1.5 ↓FPG 1.6-2.4	↓HbA1c* 1.3 ↓FPG*1.3	↓A1c* 1.27 (1.41 to 1.13) ↓FPG* 1.82 (2.07 to 1.57)
Lixisenatide	↓A1c 0.8-0.9 ↓FPG −1.1 ↓PPG −3.7	↓A1c 0.7-1.0 ↓FPG 0.6 to 0.9 ↓PPG 5.9	↓A1c 0.6-0.9 FPG -4.0 to +2.1 mg/dl	↓A1c 0.52 (0.64 to 0.39), ↓FPG 13.6 (16.71, 10.60) mg/dl
Exenatide once weekly	↓A1c ~ 1.5 ↓FPG 2.3	↓A1c 1.3 ↓FPG 28.8 mg/dL	↓A1c 1.01	↓A1c 1.59 (1.70 to 1.48) ↓FPG 2.12 (2.28 to 1.96)
Albiglutide	↓A1c 0.3-1.0 ↓FPG 1.2-1.4	↓A1c 0.36-0.63 ↓FPG 1.5	↓A1c 0.82 ↓FPG 0.5-1.0	↓A1c -0.66% (1.14 to 0.19) ↓FPG 1.54 (1.86 to 1.22)
Dulaglutide	↓A1c 0.8-1.5 ↓FPG 26 to 29 mg/dl ↓PPG 28.6 to 30 mg/dl	↓A1c 0.8-1.5 ↓FPG 30-40 mg/dl	↓A1c 1.08	↓A1c 1.18 (1.34 to 1.02) ↓FPG 1.93 (2.12 to 1.74)

*Liraglutide 1.8mg

Table 7: Summary of the impact of GLP-1 RAs on weight (kg), waist circumference (cm) and systolic BP (mmHg). Data presented as mean difference and 95%CI or ranges reported from different studies. Most of the data are derived from published meta-analyses cited in the text. NS: non-significant. 203-273

	Weight change (kg)	Waist circumference change (cm)	Systolic BP change (mmHg)
Exenatide twice-daily	Meta-analysis: -2.8; -2.9 to -2.7 Meta-analysis: -1.37; -2.22, -0.52	Meta-analysis: vs. placebo: -1.34; -2.00 to -0.75 vs. TZDs: -2.86; -4.35 to -1.60 vs. insulin: -4.02; -5.75 to -2.47	Meta-analysis: vs. placebo: -2.27; -3.27 to -1.28 vs. TZDs: NS vs. sitagliptin: NS vs. insulin: -4.23; -5.16 to -3.19
Liraglutide	Meta-analysis: -2.2; -3.5 to -0.9 Meta-analysis*: -1.51; -2.67 to -0.37 Meta-analysis$^{\$}$: -1.01; -2.41 to 0.38	Meta-analysis: vs. placebo: -5.24; -7.68 to -2.93*, and -4.73; -6.68 to -2.65$^{\$}$ vs. sitagliptin -1.73; -3.04 to -0.55* vs. TZD: -6.99; -9.47 to -4.01 vs. insulin: -8.03; -6.41 to -9.81*	Meta-analysis: vs. placebo: -2.29; -3.55 to -1.08* vs. sitagliptin: NS vs. TZD: NS vs. insulin: -4.24; -3.09 to -5.37*
Lixisenatide	0 to 2.7	Not available	
Exenatide once weekly	Meta-analysis: -2.8; -5.2 to -0.3 Meta-analysis: -1.62; -2.95 to -0.30	Meta-analysis: vs. TZD -2.69; -4.75 to -0.05 vs. insulin: -3.72; -4.60 to -2.83	Meta-analysis: vs. placebo -1.90; -3.47 to -0.45 vs. TZD: NS vs. sitagliptin: NS vs. insulin: -3.86; -5.21 to -2.53
Albiglutide	No significant weight loss vs. placebo -1.4 to -4.9 when compared to insulin or TZDs	Not available	Meta-analysis vs. placebo: -2.65; -5.19 to -0.24 vs. TZD: NS vs. sitagliptin: NS vs. insulin: -4.60; -7.18 to -2.03
Dulaglutide 1.5mg	-1.3 to -3.03	Not available	vs. placebo -2.8; -4.6 to -1.0

*Liraglutide 1.8 mg; $^{\$}$Liraglutide 1.2mg

Table 8: Summary of the head-to-head GLP-1 RA trials. Refs 168, 179, 182, 184, 196, 197, 239-241. Copied from 284. Permissions to be obtained

Study	Design	Baseline characteristics	Background therapy	Active comparators
DURATION-1 [Drucker *et al.* 2008]	R, OL, AC, NI *N*=295, 30 weeks	Mean age 55 years, A1C 8.3%, weight 102 kg, BMI 35 kg/m², duration of diabetes 6.7 years	Drug naïve or metformin, SU, TZD or a combination of two of those agents	Exenatide 10 µg BID Exenatide 2 mg QW
LEAD-6 [Buse *et al.* 2009]	R, OL, AC, NI *N*=464, 26 weeks	Mean age 57 years, A1C 8.1%, weight 93 kg, BMI 32.9 kg/m², duration of diabetes 8.2 years	metformin, SU, or both	Exenatide 10 µg BID Liraglutide 1.8 mg QD
DURATION-5 [Blevins *et al.* 2011]	R, OL, AC, NI *N*=252, 24 weeks	Mean age 56 years, A1C 8.4%, weight 96 kg, BMI 33.3 kg/m², duration of diabetes 7 years	Drug naïve or metformin, SU, TZD or any combination	Exenatide 10 µg BID Exenatide 2 mg QW
DURATION-6 [Buse *et al.* 2013]	R, OL, AC, NI *N*=911, 26 weeks	Mean age 57 years, A1C 8.5%, weight 91 kg, BMI 32.3 kg/m², duration of diabetes 8.5 years	Metformin, SU, both, or metformin + pioglitazone	Exenatide 2 mg QW Liraglutide 1.8 mg QD
GetGoal-X [Rosenstock *et al.* 2013]	R, OL, AC, NI *N*=634, 24 weeks	Mean age 57 years, A1C 8.0%, weight 95 kg, BMI 33.6 kg/m², duration of diabetes 6.8 years	Metformin	Lixisenatide 20 µg QD Exenatide 10 µg BID
HARMONY-7 [Pratley *et al.* 2014]	R, OL, AC, NI *N*=841, 32 weeks	Mean age 56 years, A1C 8.2%, weight 92 kg, BMI 32.8 kg/m², duration of diabetes 8.4 years	metformin, pioglitazone, SU, or any combination	Albiglutide 50 mg QW Liraglutide 1.8 mg QD
AWARD-1 [Wysham *et al.* 2014]	R, OL, PC, AC, S*, NI *N*=978, 26 weeks	Mean age 56 years, A1C 8.1%, weight 96 kg, BMI 33 kg/m², duration of diabetes 9 years	Metformin + pioglitazone	Dulaglutide 1.5 mg QW Dulaglutide 0.75 mg QW Exenatide 10 µg BID Placebo
AWARD-6 [Dungan *et al.* 2014]	R, OL, AC, NI *N*=599, 26 weeks	Mean age 57 years, A1C 8.1%, weight 94 kg, BMI 33.5 kg/m², duration of diabetes 7.2 years	Metformin	Dulaglutide 1.5 mg QW Liraglutide 1.8 mg QD

Abbreviations: R, randomized; OL, open label; AC, active comparator; PC, placebo controlled; S, superiority; NI, noninferiority; PC, placebo controlled; BID, twice daily; QD, once daily; QW, once weekly; SU, sulfonylurea; TZD, thiazolidinedione; BMI, body mass index.
Superiority testing *versus* placebo, noninferiority testing *versus* exenatide.

Table 9: Summary of GLP-1 RAs head-to-head trials: changes in HbA1c and body weight. Refs 206, 217, 220, 222, 232, 233, 240, 284-286.

	HbA1c change from baseline (%)	Weight change from baseline (kg)	Comments on Adverse events
DURATION-1 Exenatide QW vs. Exenatide BD	–1.9 vs. –1.5 95% CI –0.54, –0.12, p = 0.0023	–3.7 kg vs. –3.6 kg p=0.89	Exenatide BD: Higher incidence of nausea and vomiting Exenatide QW: more injection-site reactions
LEAD-6 Liraglutide vs. exenatide BD	–1.12 vs. –0.79 95% CI –0.47, –0.18 p < 0.0001	–3.24 kg vs. 2.87 kg, p = 0.22	More adverse events with exenatide but more serious adverse events with liraglutide
DURATION-5 Exenatide QW vs. Exenatide BD	–1.6 vs –0.9 95%CI −0.9, −0.4 p < 0.0001	-2.3 vs. -1.4 p non-significant	Similar to DURATION-1
DURATION-6 Liraglutide vs. Exenatide QW	–1.48 vs. –1.28 95% CI 0.08, 0.33 p = 0.02 (predefined non-inferiority criteria were not met)	–3.57 vs. –2.68 p = 0.0005	Liraglutide: higher rates of nausea, vomiting, and diarrhoea Exenatide QW: more injection site reactions
GetGOAL X Lixisenatide vs. Exenatide BD	–0.79 vs. –0.96% 95% CI 0.033–0.297 Pre-defined non-inferiority criteria were met	–2.96 vs.–3.98 95% CI, 0.456–1.581 In favour of exenatide	Less nausea and less hypoglycaemia with lixisenatide treatment
HARMONY-7 Liraglutide vs. Albiglutide	0.99 vs. 0.78 95% CI 0.08, 0.34 p = 0.0846 Pre-defined non-inferiority criteria were not met	–2.16 and –0.64 p < 0.0001	Liraglutide: slightly more nausea and vomiting Albiglutide: more injection site reactions
AWARD-1 Dulaglutide 1.5mg vs. Dulaglutide 0.75mg vs. Exenatide BD	–1.51% vs. –1.30% vs. –0.99% vs. –0.46% (p < 0.001 for both dulaglutide doses vs. exenatide)	–1.30 vs. +0.2 vs. –1.07 vs. +1.24 (p=0.47 for dulaglutide 1.5mg vs. exenatide)	No differences between dulaglutide and exenatide

vs. placebo			
AWARD-6 Dulaglutide vs. Liraglutide	–1.42 vs. –1.36 95% CI –0.19, 0.07 , predefined non-inferiority criteria was met	–2.90 vs. –3.61 p = 0.011	No differences between groups

Table 10: Pharmacokinetics of SGLT-2 inhibitors. Adapted from Tahrani et al 2013 (Ref 295

	Dose (mg)	IC_{50} SGLT1 vs. 2	T_{max} (h)	C_{max}	$t_{1/2}$ (h)	Comments
Dapagliflozin	10	1390 vs. 1.1 nM Ratio ~1300:1	1.5-2.0	~160 ng/ml	~13	Steady state, healthy subjects
Canagliflozin	100 300	684 vs. 2.2 nM Ratio ~300:1	~1.5 ~1.9	~1.0 ug/ml 2.7 ug/ml	10.6 13.1	Single dose, type 2 diabetes
Empagliflozin	10 25	8300 vs. 3.1 nM Ratio ~2700:1	1.5 1.5	259 nmol/l 687 nmol/l	13.2 13.3	After 28 days, type 2 diabetes

Figure 1: This figure illustrates key organs involved in the pathogenesis of type 2 diabetes and indicates important sites of action of blood glucose-lowering agents, underpinned by lifestyle measures. Agents on a pink background are prone to cause weight gain, a yellow background indicates weight neutral and a green background indicates weight loss. A black perimeter indicates greater risk of precipitating hypoglycaemia.
Multiple genetic and environmental factors give rise to type 2 diabetes mellitus (T2DM) through insulin resistance with pancreatic β-cell failure . Overweight and obesity contribute to insulin resistance in association with increased inflammatory signals and disturbed lipid homeostasis, often preceding the onset of hyperglycaemia by many years and enhancing cardiovascular risk. When insulin secretion is no longer sufficient to overcome insulin resistance, glucose intolerance progresses to T2DM, usually accompanied by pancreatic α-cell dysfunction that elevates glucagon secretion, reduced prandial secretion or activity of incretin hormones such as GLP-1, likely alterations to the gut microbiome and disturbances of neural activities controlling hunger-satiety and the circadian regulation of glucose homeostasis. This figure was adapted from Tahrani et al Lancet 2011, 378, 182–197 and DeFronzo Diabetes 2009;**58**:773–95 with permission.

Fig 1

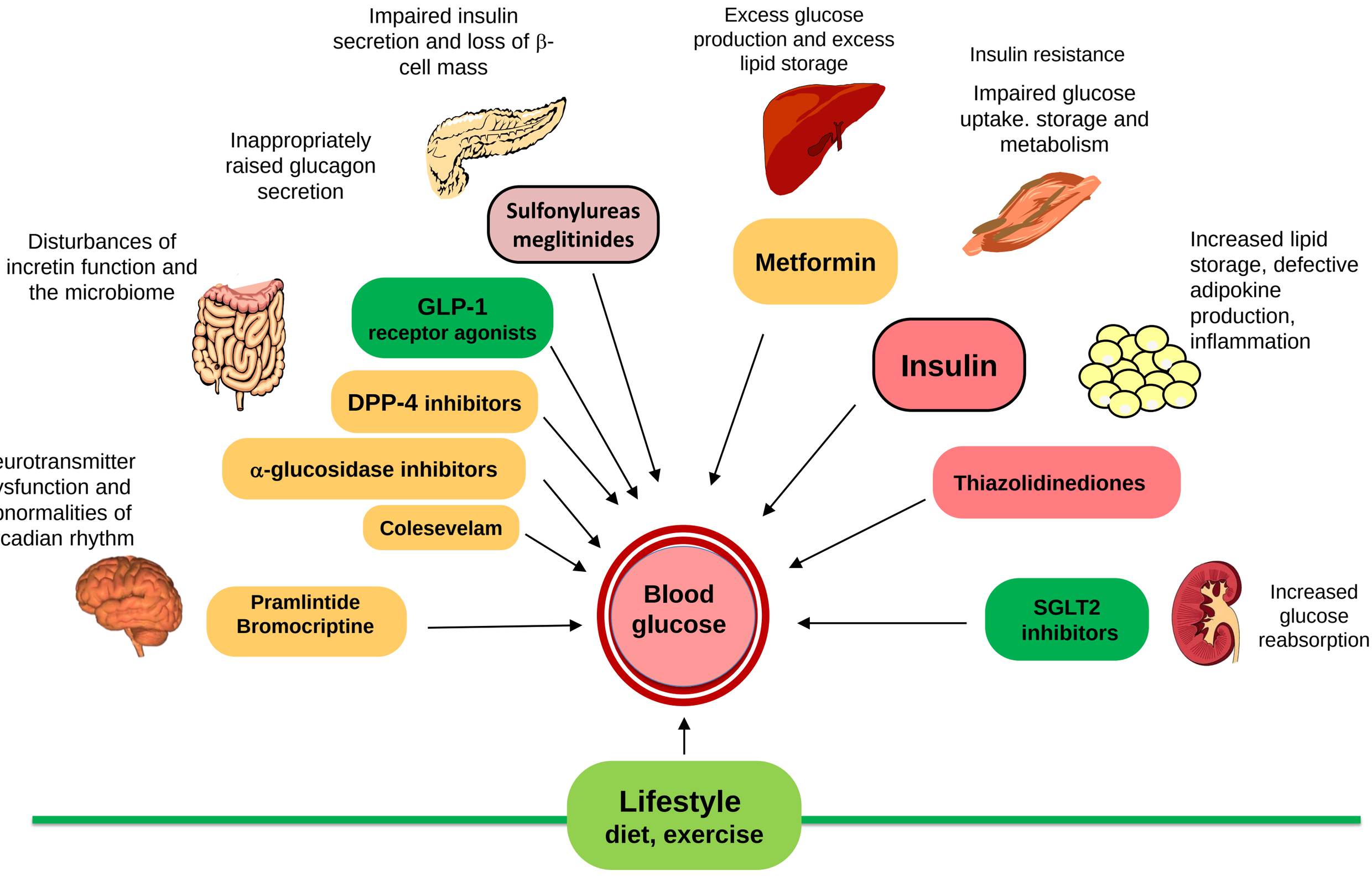
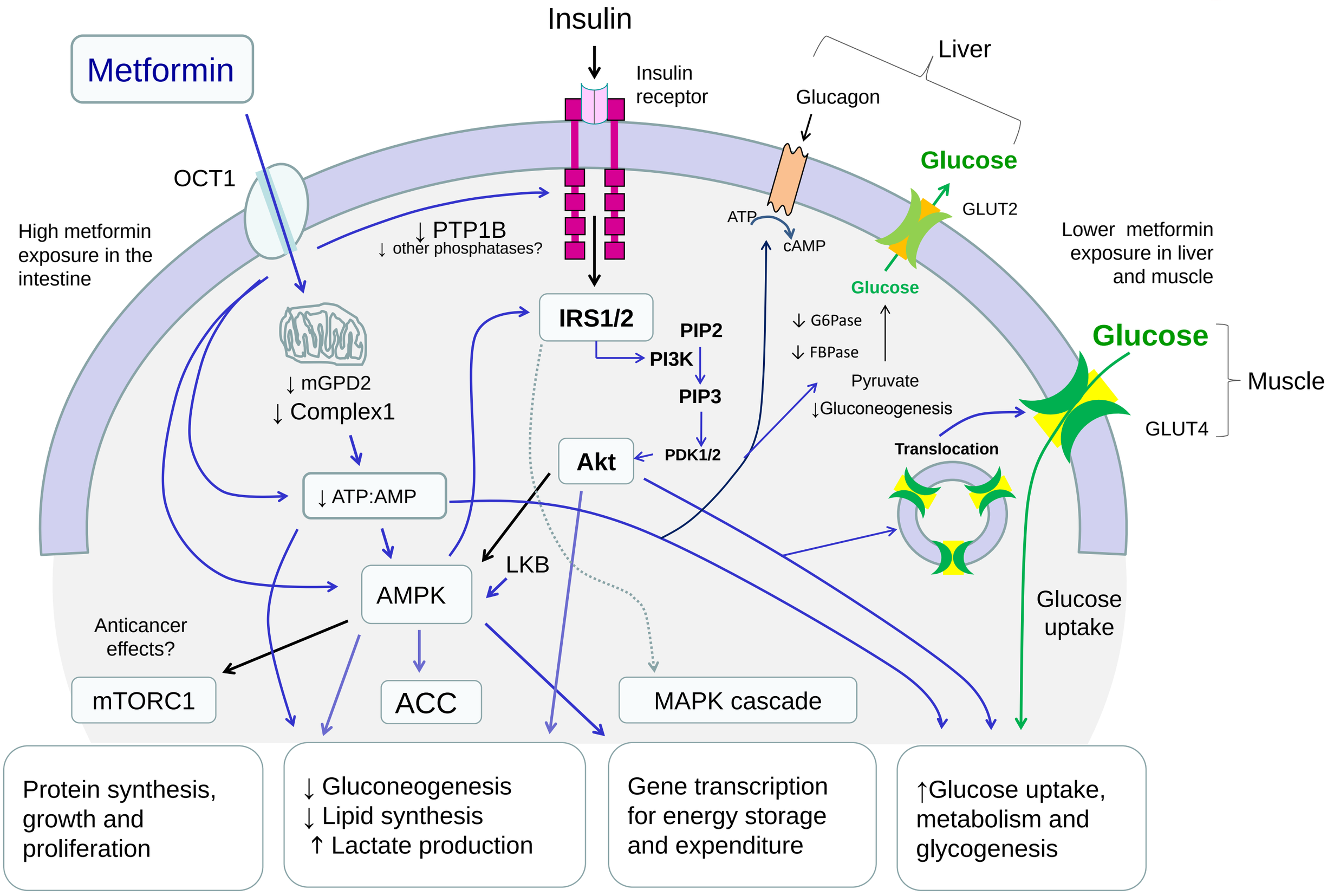

Impaired insulin secretion and loss of β-cell mass
Inappropriately raised glucagon secretion
Sulfonylureas meglitinides
Excess glucose production and excess lipid storage
Insulin resistance
Impaired glucose uptake. storage and metabolism
Metformin
Disturbances of incretin function and the microbiome
GLP-1 receptor agonists
DPP-4 inhibitors
Insulin
Increased lipid storage, defective adipokine production, inflammation
α-glucosidase inhibitors
Thiazolidinediones
Neurotransmitter dysfunction and abnormalities of circadian rhythm
Colesevelam
Blood glucose
Pramlintide Bromocriptine
SGLT2 inhibitors
Increased glucose reabsorption
Lifestyle
diet, exercise

Figure 2. Intracellular actions of metformin. Metformin alters nutrient metabolism through insulin dependent and independent effects which vary with the amount of drug exposure and the activity of insulin within different tissues. For example, the intestine is exposed to very high concentrations of metformin which exert insulin independent effects, whereas liver and muscle are exposed to lower concentrations of metformin that influence the metabolic effects of insulin. Metformin can improve insulin sensitivity via effects on insulin receptor signalling and post-receptor signalling pathways of insulin action. Metformin can alter cellular nutrient metabolism and energy production independently of insulin via suppression of the mitochondrial respiratory chain and activation of adenosine 5′-monophosphate-activated protein kinase (AMPK). ACC, acetyl CoA carboxylase; Akt , protein kinase B (PKB); AMPK, adenosine monophosphate-activated protein kinase; FBPase, fructose 1,6-bisphosphatase; G6Pase, glucose 6-phosphatase; GLUT, glucose transporter isoform; IRS, insulin receptor substrate; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; PDK, phosphoinositide-dependent protein kinase; PI3K, phosphatidylinositol 3-kinase; PIP2, phosphatidylinositol-3,4-bisphosphate; PIP3, phosphatidylinositol-3,4,5-trisphosphate; Oct1, organic cation transporter 1; LKB1, LKB1 protein kinase; mGPD2, mitochondrial glycerol-3-phoshate dehydrogenase-2. Adapted from Bailey CJ. Nature Rev Endocrinol, 2012, 5, 651-2. Doi. 10.1038/nrend 2012.106.

One of the present authors has recently submitted a similar (not identical) version of this illustration for the 5th edition of Textbook of Diabetes (Wiley) which is due for publication in 2016

Fig 2



Adapted from Bailey CJ. Nature Rev Endocrinol, 2012, 106. Doi. 10.1038/nrend 2012.106

Figure 3: Sulfonylureas and meglitinides act on pancreatic β-cells to stimulate insulin secretion. These agents bind to the cytosolic surface of the sulfonylurea receptor 1 (SUR1) which is part of the ATP-sensitive Kir6.2 potassium channel. Binding of the sulfonylurea or meglitinide closes the Kir6.2 channel, preventing potassium efflux and depolarizing the plasma membrane. This opens local voltage-dependent calcium channels, increasing the influx of calcium and activating calcium-dependent signalling proteins that control insulin exocytosis. GPR40 agonists in development stimulate insulin secretion by raising cytosolic calcium mainly via PLC-IP3-mediated redistribution of calcium from the endoplasmic reticulum and PKC-mediated effects on granule exocytosis. GLP-1 receptor agonists enhance nutrient-induced insulin release mainly via a cAMP-Epac2-mediated potentiation of granule exocytosis. cAMP, cyclic adenosine monophosphate; EPAC2, cAMP-regulated guanine nucleotide exchange factor-2; GLUT, glucose transporter isoform; IP3, inositol-1,4,5-trisphosphate; Piccolo, calcium sensitive cytoskeleton matrix-associated active zone protein; Rab3A, a GTP-binding protein; Rap1, a Ras-related GTPase; Rim2, an insulin granule-associated protein; PKA, protein kinase A; PLC, phospholipase C. Adapted from Bailey , Lancet, 2012, 379, p. 1370-1371.

Note to editor. Reviewer 1 asked for detailed information on the effect of sulfonylureas on the Epac pathway. Although we have included information that we feel is verified, a role of sulfonylureas on the SUR1 molecules expressed on insulin granule membranes and their interaction with the Epac2-Piccolo-Rim complex to drive exocytosis through charge (eg Cl-) alterations remain under investigation and we are reluctant to go into more detail on the pros and cons for this type of article, as we think it would not be welcomed by the non-specialist non-scientist reader. .

Fig 3

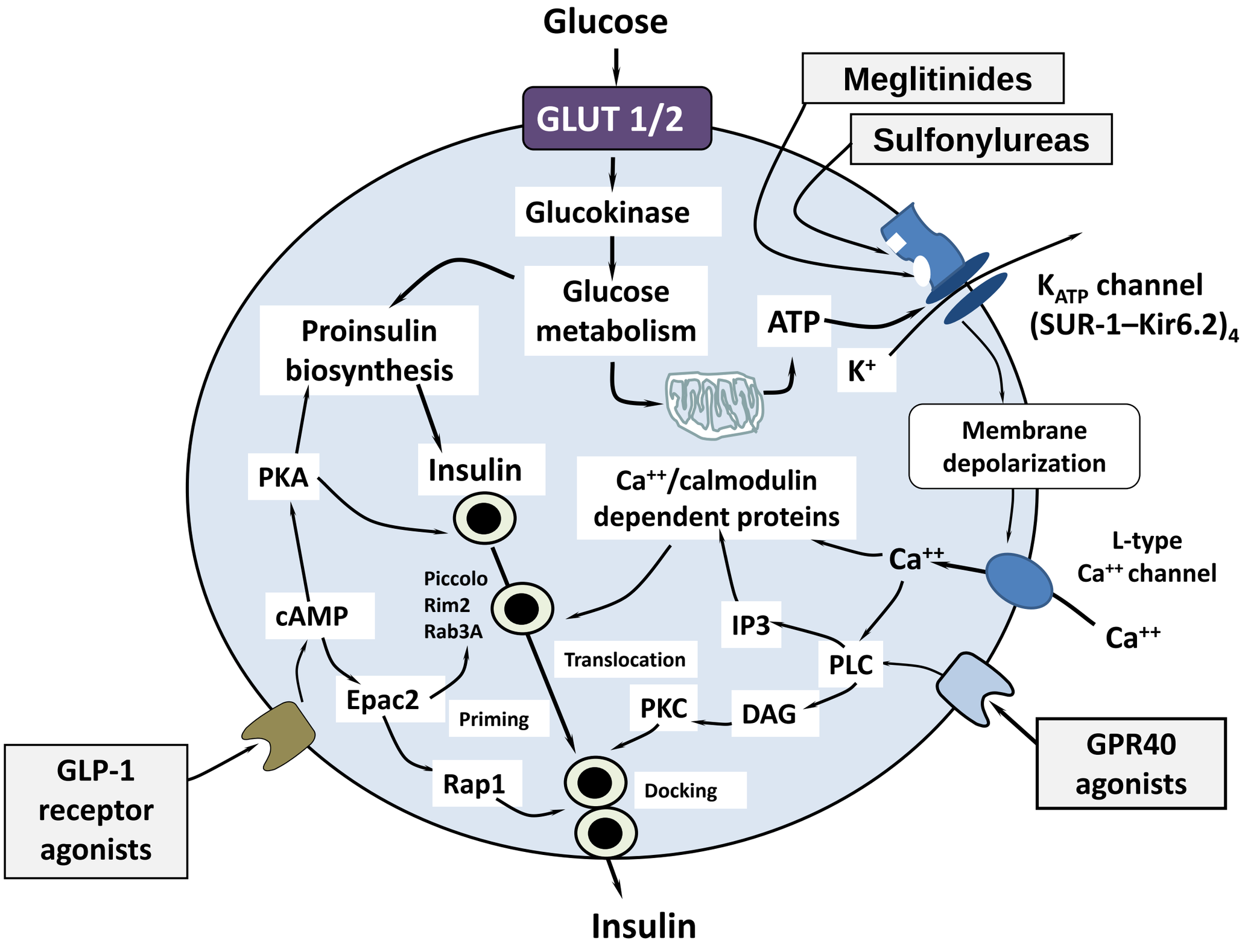

Glucose
GLUT 1/2
Glucokinase
Glucose metabolism
Proinsulin biosynthesis
PKA
Insulin
cAMP
Piccolo
Rim2
Rab3A
Epac2
Translocation
Priming
Rap1
Docking
Insulin
Meglitinides
Sulfonylureas
ATP
K+
KATP channel
(SUR-1–Kir6.2)4
Membrane depolarization
Ca++/calmodulin dependent proteins
Ca++
L-type Ca++ channel
Ca++
IP3
PLC
PKC
DAG
GPR40 agonists
GLP-1 receptor agonists

Figure 4: Cellular mechanism of action of thiazolidinediones. Most actions of a thiazolidinedione (TZD) are mediated via stimulation of the nuclear peroxisome proliferator-activated receptor - gamma (PPAR-γ), which is highly expressed in adipose tissue. When stimulated, PPAR-γ forms a heterodimeric complex with the retinoid X receptor (RXR). The complex binds to the peroxisome proliferator response element (PPRE) nucleotide sequence (AGGTCAXAGGTCA) in the promoter regions of certain genes, recruits co-activators, and alters the transcriptional activity of these genes. This modifies nutrient uptake and metabolism, as well as the other functions of the cell. RXR, retinoid X receptor; GLUT4, glucose transporter isoform 4; FATP, fatty acid transport protein; LPL, lipoprotein lipase. Adapted from Tahrani et al, Lancet 2011, 378, 182–197

Fig 4

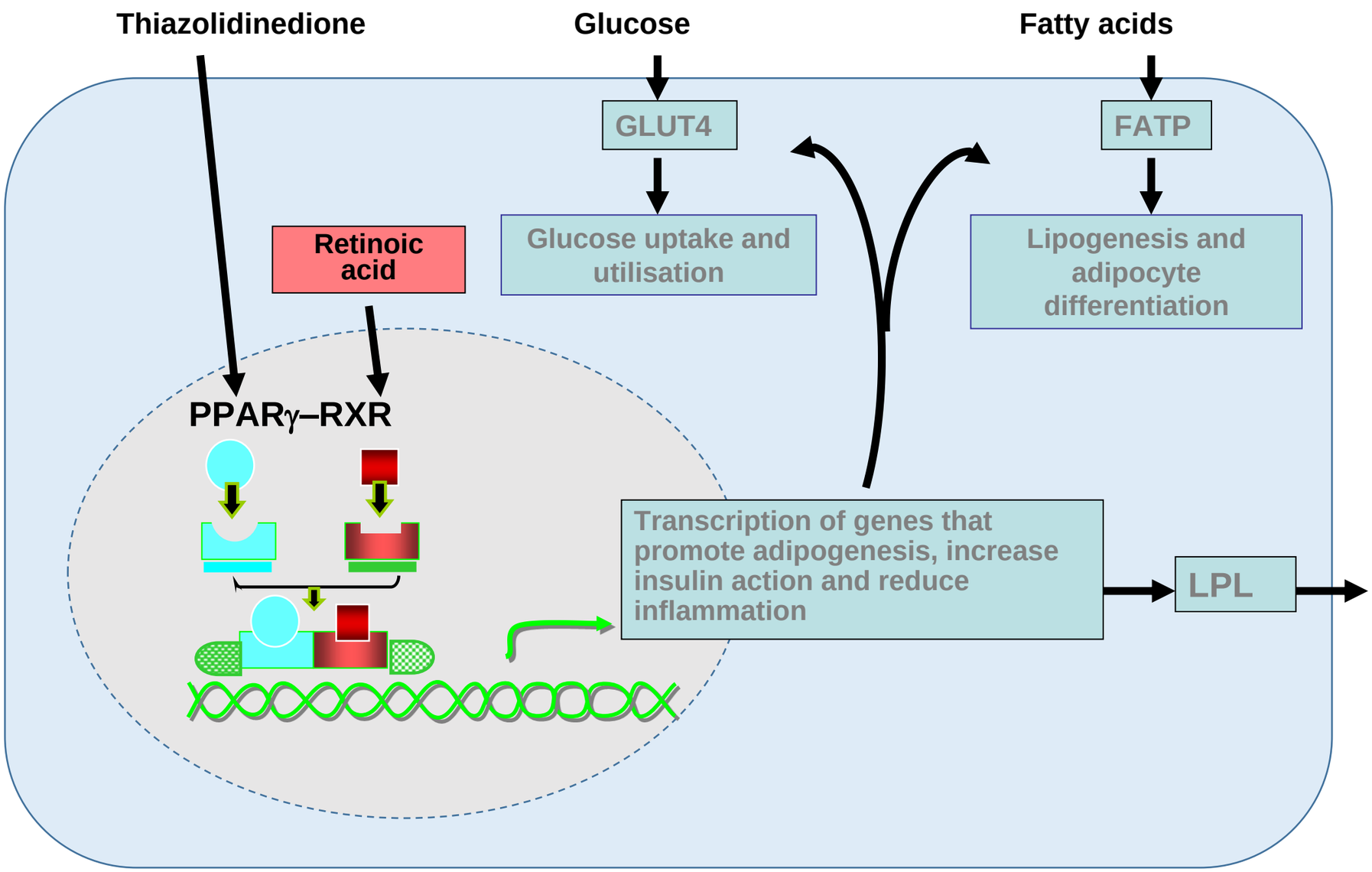
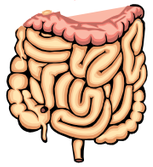

Thiazolidinedione
Glucose
Fatty acids
GLUT4
FATP
Retinoic acid
Glucose uptake and utilisation
Lipogenesis and adipocyte differentiation
PPARγ–RXR
Transcription of genes that promote adipogenesis, increase insulin action and reduce inflammation
LPL

Figure 5: Pancreatic and extra-pancreatic effects of glucagon-like peptide-1. Some actions are still controversial in man and are shown with a question mark. ↑ increase; ↓ decrease.

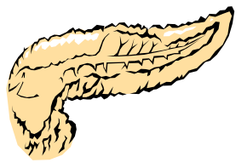
Fig 5



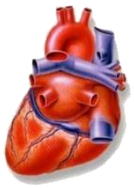
L-cells

GLP-1

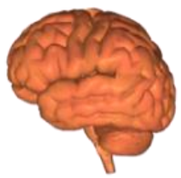
Pancreas
↑ Glucose-induced insulin secretion
↑ Proinsulin biosynthesis
↑ Beta-cell survival
↓ Glucagon secretion



Heart
↑ Heart rate
↑ **M**yocardial contractility
↓ Ischaemic damage to myocardium ?



Brain
↑ Satiety → weight loss
Neuroprotection
↑ Neurogenesis

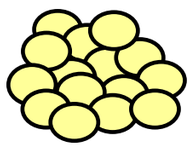


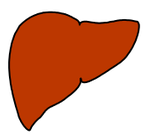
Kidney
↑ Sodium elimination
(↓ Na^+-H^+ exchanger (NHE3) in proximal tubules)

Stomach
Delay gastric emptying

Arteries
↑ Endothelial-dependent vasodilatation
↓ BP

Adipose tissue
↑Lipolysis
Thermogenesis
Energy expenditure





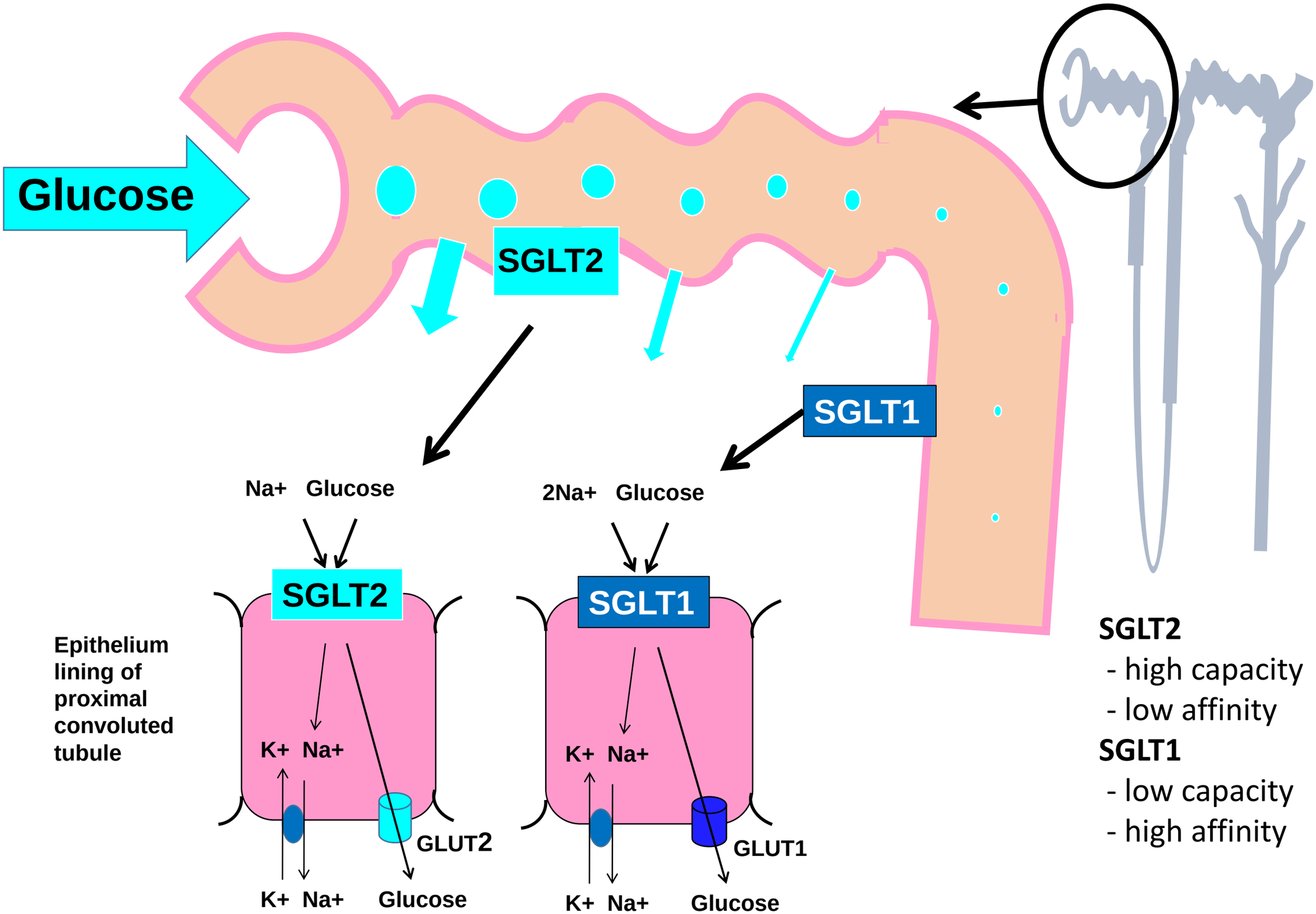
Liver
↑ Glycogen storage
↑ Hepatic insulin extraction ?

Inflammation
Anti-inflammatory effect

Muscle
↑ Glucose uptake?

Figure 6. Glucose handling via sodium glucose co-transporter (SGLT) proteins SGLT-2 and SGLT-1 in the kidney; GLUT: Glucose Transporter. Adapted from Bailey CJ, Day C. Br J Diabetes Vasc Dis 2010; 10: 193-9.

Fig 6



SGLT2
- high capacity
- low affinity

SGLT1
- low capacity
- high affinity