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# IDENTIFICATION OF NOVEL TARGETS OF NEW INSULIN SENSITIZERS- STUDIES OF RELATED MECHANISM WITH OTHER GLUCOSE-LOWERING AGENTS

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## ABSTRACT

**Aims: To** explains novel targets of currently used and new insulin sensitizers with emphasis on Sodium-glucose cotransporter-2 (SGLT-2) inhibitors, G-protein-coupled receptors (GPCRs), thiazolidinediones, insulin secretogogues, and stem cell therapy. **Method:** Review of recent literature that emphasizes on novel targets and techniques belonging to glucose-lowering drugs and therapeutic intervention especially those studies that focus on new insulin sensitizers. **Results and conclusion:** Diabetes is a global major health problem that needs challenging and renewable medications every day as we need to individualize both treatment targets and treatment strategies. Identification of novel targets and techniques for therapeutic intervention will lead to more personalized approaches to treatment and hence to define which medication to be used in whom with regard to benefits and side effects.

**KEYWORDS:** Sodium-glucose cotransporter-2 (SGLT-2) inhibitors; G-protein-coupled receptors (GPCRs); Metformin; Thiazolidinediones; Glucagon-like peptide-1 (GLP-1); Peroxisome proliferator-activated receptors (PPARs).

**Background:** Diabetes is a major health problem; approximately more than 5% of the world's population suffers from diabetes. Independent forecasters have suggested that the

global prevalence of the disease will increase from 150 m in 2000 to 220 m in 2010 and to 300 m by 2025[1]. Treatment of hyperglycemia in patients with type 2 diabetes remains a challenge, particularly in those who require insulin as the disease progresses.[2,3]

Glycemic management in type 2 diabetes mellitus has become increasingly complex and, to some extent, controversial, with a widening array of pharmacological agents now available[4]. It is clear that the contributory abnormalities in type 2 DM are insulin deficiency, insulin resistance and increased hepatic glucose output. With this in mind, therapies used to treat patients with this disease are aimed at correcting one or more of these physiological abnormalities.[1]

Diabetes is a complex, chronic illness requiring continuous medical care with multifactorial risk-reduction strategies beyond glycemic control. Ongoing patient self-management education and support are critical to preventing acute complications and reducing the risk of long-term complications. Significant evidence exists that supports a range of interventions to improve diabetes outcomes.[5]

**Insulin resistance**

Under normal physiological conditions, plasma glucose concentrations are maintained within a narrow range, despite wide fluctuations in supply and demand, through a tightly regulated and dynamic interaction between tissue sensitivity to insulin (especially in the liver) and insulin secretion. In type 2 diabetes, both of these mechanisms break down with impaired insulin secretion through pancreatic β-cell dysfunction and impaired insulin action through insulin resistance. Insulin resistance is the inability of insulin to produce its usual biological effects at physiological concentrations and it is a cardinal feature of type 2 diabetes.[6]

**Glucose lowering agents in type 2 diabetes**

Impaired insulin secretion, increased hepatic glucose production, and decreased peripheral glucose utilization are the core defects responsible for the development and progression of type 2 diabetes. However, the pathophysiology of this disease also includes adipocyte insulin resistance (increased lipolysis), reduced incretin secretion/sensitivity, increased glucagon secretion, enhanced renal glucose reabsorption, and brain insulin resistance/neurotransmitter dysfunction. Although current diabetes management focuses on lowering blood glucose, the goal of therapy should be to delay disease progression and eventual treatment failure. Recent

innovative treatment approaches target the multiple pathophysiological defects present in type 2 diabetes.[7]

Properties of available glucose-lowering agents in the U.S. and Europe that may guide individualized treatment choices in patients with type 2 diabetes are summarized in table 1.

**Table 1: Properties of available glucose-lowering agents in the U.S. and Europe that may guide individualized treatment choices in patients with type 2 diabetes**

| Class | Compound(s) | Cellular mechanism(s) | Primary physiological action(s) | Advantages | Disadvantages | Cost* |
|---|---|---|---|---|---|---|
| Biguanides | • Metformin | Activates AMP-kinase (? other) | • ↓ Hepatic glucose production | • Extensive experience | • Gastrointestinal side effects (diarrhea, abdominal cramping) | Low |
| | | | | • No hypoglycemia | • Lactic acidosis risk (rare) | |
| | | | | • ↓ CVD events (UKPDS) | • Vitamin $B_{12}$ deficiency | |
| | | | | | • Multiple contraindications: CKD, acidosis, hypoxia, dehydration, etc. | |
| Sulfonylureas | 2nd Generation | Closes $K_{ATP}$ channels on β-cell plasma membranes | • ↑ Insulin secretion | • Extensive experience | • Hypoglycemia | Low |
| | • Glyburide/glibenclamide | | | • ↓ Microvascular risk (UKPDS) | • ↑ Weight | |
| | • Glipizide | | | | • ? Blunts myocardial ischemic preconditioning | |
| | • Gliclazide† | | | | • Low durability | |
| | • Glimepiride | | | | | |
| Meglitinides (glinides) | • Repaglinide | Closes $K_{ATP}$ channels on β-cell plasma membranes | • ↑ Insulin secretion | • ↓Postprandial glucose excursions | • Hypoglycemia | Moderate |
| | • Nateglinide | | | • Dosing flexibility | • ↑ Weight | |
| | | | | | • ? Blunts myocardial ischemic preconditioning | |
| | | | | | • Frequent dosing schedule | |
| TZDs | • Pioglitazone‡ | Activates the nuclear transcription factor PPAR-γ | • ↑ Insulin sensitivity | • No hypoglycemia | • ↑ Weight | Low |
| | • Rosiglitazone§ | | | • Durability | • Edema/heart failure | |
| | | | | • ↑ HDL-C | • Bone fractures | |
| | | | | • ↓ Triglycerides | • ↑ LDL-C (rosiglitazone) | |

| Class | Compound(s) | Cellular mechanism(s) | Primary physiological action(s) | Advantages | Disadvantages | Cost* |
|---|---|---|---|---|---|---|
| | | | | (pioglitazone) | | |
| | | | | • ? ↓ CVD events (PROactive, pioglitazone) | • ? ↑ MI (meta-analyses, rosiglitazone) | |
| α-Glucosidase inhibitors | • Acarbose | Inhibits intestinal α-glucosidase | • Slows intestinal carbohydrate digestion/absorption | • No hypoglycemia | • Generally modest $HbA_{1c}$efficacy | |
| | • Miglitol | | | • ↓Postprandial glucose excursions | | |
| | | | | • ? ↓ CVD events (STOP-NIDDM) | • Gastrointestinal side effects (flatulence, diarrhea) | |
| | | | | • Nonsystemic | • Frequent dosing schedule | Moderate |
| DPP-4 inhibitors | • Sitagliptin | Inhibits DPP-4 activity, increasing postprandial active incretin (GLP-1, GIP) concentrations | • ↑ Insulin secretion (glucose-dependent) | • No hypoglycemia | • Angioedema/urticaria and other immune-mediated dermatological effects | |
| | • Vildagliptin† | | • ↓ Glucagon secretion (glucose-dependent) | • Well tolerated | • ? Acute pancreatitis | |
| | • Saxagliptin | | | | | |
| | • Linagliptin | | | | • ? ↑ Heart failure hospitalizations | |
| | • Alogliptin | | | | | High |
| Bile acid sequestrants | • Colesevelam | Binds bile acids in intestinal tract, increasing hepatic bile acid production | • ? ↓ Hepatic glucose production | • No hypoglycemia | • Generally modest $HbA_{1c}$efficacy | |
| | | | • ? ↑ Incretin levels | • ↓ LDL-C | • Constipation | |
| | | | | | • ↑ Triglycerides | |
| | | | | | • May ↓ absorption of other medications | High |
| Dopamine-2 agonists | • Bromocriptine (quick release)§ | Activates dopaminergic receptors | • Modulates hypothalamic regulation of metabolism | • No hypoglycemia | • Generally modest $HbA_{1c}$efficacy | |
| | | | | | • Dizziness/syncope | High |

| Class | Compound(s) | Cellular mechanism(s) | Primary physiological action(s) | Advantages | Disadvantages | Cost* |
|---|---|---|---|---|---|---|
| | | | • ↑ Insulin sensitivity | • ? ↓ CVD events (Cycloset Safety Trial) | • Nausea | |
| | | | | | • Fatigue | |
| | | | | | • Rhinitis | |
| SGLT2 inhibitors | • Canagliflozin | Inhibits SGLT2 in the proximal nephron | • Blocks glucose reabsorption by the kidney, increasing glucosuria | • No hypoglycemia | • Genitourinary infections | High |
| | • Dapagliflozin‡ | | | • ↓ Weight | • Polyuria | |
| | • Empagliflozin | | | | • Volume depletion/hypotension/dizziness | |
| | | | | • ↓ Blood pressure | • ↑ LDL-C | |
| | | | | • Effective at all stages of T2DM | • ↑ Creatinine (transient) | |
| GLP-1 receptor agonists | • Exenatide | Activates GLP-1 receptors | • ↑ Insulin secretion (glucose-dependent) | • No hypoglycemia | • Gastrointestinal side effects (nausea/ vomiting/diarrhea) | High |
| | • Exenatide extended release | | • ↓ Glucagon secretion (glucose-dependent) | | • ↑ Heart rate | |
| | • Liraglutide | | | • ↓ Weight | • ? Acute pancreatitis | |
| | • Albiglutide | | • Slows gastric emptying | • ↓ Postprandial glucose excursions | • C-cell hyperplasia/medullary thyroid tumors in animals | |
| | • Lixisenatide† | | • ↑ Satiety | • ↓ Some cardiovascular risk factors | • Injectable | |
| | • Dulaglutide | | | | • Training requirements | |
| Amylin mimetics | • Pramlintide§ | Activates amylin receptors | • ↓ Glucagon secretion | • ↓ Postprandial glucose excursions | • Generally modest $HbA_{1c}$efficacy | High |
| | | | • ↑ Satiety | • ↓ Weight | • Gastrointestinal side effects (nausea/ vomiting) | |
| | | | | | • Hypoglycemia unless insulin dose is simultaneously reduced | |
| | | | • Slows gastric emptying | | • Injectable | |
| | | | | | • Frequent dosing schedule | |

| Class | Compound(s) | Cellular mechanism(s) | Primary physiological action(s) | Advantages | Disadvantages | Cost* |
|---|---|---|---|---|---|---|
| | | | | | • Training requirements | |
| Insulins | • Rapid-acting analogs | Activates insulin receptors | • ↑ Glucose disposal | • Nearly universal response | • Hypoglycemia | Variable# |
| | - Lispro | | | | | |
| | - Aspart | | | | | |
| | - Glulisine | | | | | |
| | • Short-acting | | | | | |
| | - Human Regular | | | | • Weight gain | |
| | • Intermediate-acting | | | | | |
| | - Human NPH | | | | | |
| | • Basal insulin analogs | | • ↓ Hepatic glucose production | • ↓ Microvascular risk (UKPDS) | • ? Mitogenic effects | |
| | - Glargine | | | | • Injectable | |
| | - Detemir | | | | • Training requirements | |
| | - Degludec† | | • Other | • Theoretically unlimited efficacy | • Patient reluctance | |
| | • Premixed (several types) | | | | | |

(Adapted from Inzucchi *et al*, 2015)[8].

There is growing evidence that therapeutic interventions that slow or delay the progression of β-cell failure can lead to more durable glycemic control. Currently available antidiabetic agents target multiple pathophysiological mechanisms present in type 2 diabetes (figure 1)[7]. Some glucose-lowering drugs or strategies adversely affect cardiovascular outcomes. Udell *et al* (2015) searched Ovid Medline, the Cochrane Library, and meeting abstracts up to Feb 20, 2015, for large randomized controlled trials of glucose-lowering drugs or strategies that assessed cardiovascular outcomes. The primary endpoint was incidence of heart failure. They derived pooled risk ratios (RRs) with random-effects models. Data from 14 trials, with mean duration 4·3 (2·3) years, comprising 95 502 patients, of whom 3907 (4%) patients developed a heart failure event. Glucose-lowering drugs or strategies were associated with a 0·50% (SD 0·33) reduction in HbA1c and a 1·7 kg (2·8) weight gain. Overall, glucose-lowering drugs or strategies increased the risk of heart failure compared with standard care (RR 1·14, 95% CI 1·01–1·30; p=0·041). The magnitude of this effect varied dependent on the method of glucose lowering (p for interaction=0·00021). Across drug classes, risk was highest with peroxisome proliferator-activated receptor agonists (RR 1·42, 95% CI 1·15–1·76; six trials), intermediate with dipeptidyl peptidase-4 inhibitors (1·25, 1·08–1·45; two trials), and neutral with insulin glargine (0·90, 0·77–1·05; one trial). Target-based intensive glycaemic control strategies (RR 1·00, 95% CI 0·88–1·13; four trials) and intensive weight loss (0·80, 95% CI 0·62–1·04; one trial) were also not associated with development of heart failure. Meta-regression analysis showed that for every 1·0 kg of weight gain associated with glucose-lowering drugs or strategies, there was a 7·1% (95% CI 1·0–13·6) relative increase in the risk of heart failure compared with standard care (p=0·022)[9].

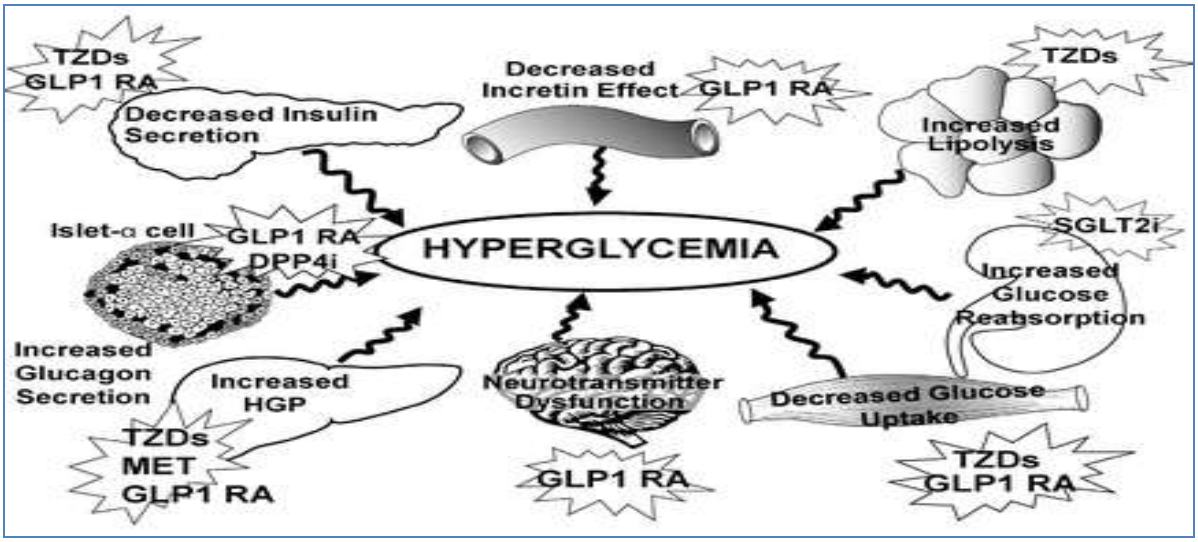


**Figure 1: Pathophysiological issues targeted by different current anti-diabetic medications (adapted from DeFronso *et al*, 2014)**

**Sodium-glucose co-transporter 2 (SGLT-2) inhibitors**

SGLT2 is a low-affinity, high capacity glucose transporter located in the proximal convoluted tubule in the kidneys. It is responsible for 90% of glucose reabsorption. Inhibition of SGLT2 leads to the decrease in blood glucose due to the increase in renal glucose excretion. The mechanism of action of this new class of drugs also offers further glucose control by allowing increased insulin sensitivity and uptake of glucose in the muscle cells, decreased gluconeogenesis and improved first phase insulin release from the beta cells. Drugs in the SGLT2 inhibitors class include empagliflozin, canagliflozin, dapagliflozin, ipragliflozin. Dapagliflozin, an SGLT2 inhibitor recently approved in Europe for the treatment of T2DM, improves glycaemic control in patients with T2DM when used as monotherapy or when added to other diabetes medications, such as metformin, sulfonylureas, pioglitazone, and insulin[10]. SGLT-2 for patients with T2DM have the potential to reduce cardiovascular (CV) risk. One review focused on the potential of a new class of antidiabetic agents, the sodium glucose cotransporter 2 (SGLT2) inhibitors, to reduce CV risk in patients with T2DM through reductions in hyperglycemia, blood pressure (BP), and body weight[11]. Hence, SGLT2 inhibitors may present an attractive option for T2DM patients who are failing with metformin monotherapy, especially if weight is part of the underlying treatment consideration[12]. Their use is also associated with reductions in plasma uric acid levels and albuminuria[13], although the clinical impact of these changes over time is unknown. Side effects of SGLT2 inhibitor therapy include genital mycotic infections, at rates of about 11% higher in women and about 4% higher in men compared with placebo. They also possess a diuretic effect, and so symptoms related to volume depletion may occur. Reversible small increases in serum creatinine occur. Increased urine calcium excretion has been observed[8]. When these related symptoms are considered collectively, up to 20–30% of women may be affected, with lower proportions of men. How much these symptoms will affect long-term adherence to treatment remains unclear, although the reports from the randomized studies suggest that in most cases the symptoms did not lead to discontinuation. Less common but also important is the potential for postural hypotension due to sodium depletion, especially in the context of diuretic therapy. Whether this effect will prove a serious risk for ill and older patients is also unknown. In one recently reported study of dapagliflozin, over 44% of the participants were older than 65 and 7% over 75 years of age. The study did suggest that when added to a usual background regimen in an older population with advanced type 2 diabetes and preexisting cardiovascular disease the SGLT2 inhibitor improved glycemic control

without an increase in hypoglycemic risk, promoted weight loss, and was reported to be well tolerated[14,15].

Vasilakou et al (2013) compared SGLT2 with placebo in 45 studies (*n* = 11 232) and with active comparators in 13 studies (n = 5175). They had a favorable effect on hemoglobin-A1c level (mean difference *vs.* placebo, −0.66% [95% CI, −0.73% to −0.58%]; mean difference *vs.* active comparators, −0.06% [CI, −0.18% to 0.05%]). Sensitivity analyses incorporating unpublished data showed similar effect estimates. Compared with other agents, SGLT2 inhibitors reduced body weight (mean difference, −1.80 kg [CI, −3.50 to −0.11 kg]) and systolic blood pressure (mean difference, −4.45 mm Hg [CI, −5.73 to −3.18 mm Hg]). Urinary and genital tract infections were more common with SGLT2 inhibitors (odds ratios, 1.42 [CI, 1.06 to 1.90] and 5.06 [CI, 3.44 to 7.45], respectively). Hypoglycemic risk was similar to that of other agents. Results for cardiovascular outcomes and death were inconclusive. An imbalance in incidence of bladder and breast cancer was noted with dapagliflozin compared with control.[16]

Taylor and Harris (2013) reviewed abstracts and published data from human trials evaluating the efficacy and safety of dapagliflozin, canagliflozin, and empagliflozin through February 2013. Data from these trials suggest that SGLT-2 inhibitors are able to lower hemoglobin A1c and fasting blood glucose when used as either monotherapy or combination therapy. Cardiometabolic benefits included a reduction in systolic blood pressure, reduction in triglycerides, and weight loss of up to 3 kg. Common and serious adverse effects including infections, cancer, and pollakiuria were identified and reviewed. Although these agents have generally demonstrated efficacy, the adverse effects associated with dapagliflozin have caused a delay in its regulatory approval. Continued research in this area will determine the risk:benefit ratio of SGLT-2 inhibitor therapy.[17]

Moreover, a novel approach to SGLT inhibition involves not only actions on SGLT2 but also blockade of SGLT1, the primary transporter for glucose uptake from intestinal lumen. The main effect of SGLT1 inhibition is expected to be a reduction in postprandial glucose. Concerning this possibility, Rosenstock *et al* (2015)[18] present data on a novel dual inhibitor of SGLT1 and SGLT2 (LX4211) in type 2 diabetes. People with type 2 diabetes inadequately controlled on metformin were randomly assigned to LX4211 in doses of 75 mg q.i.d., 200 mg q.i.d., 400 mg q.i.d., or 200 mg b.i.d. or to placebo. The new drug markedly significantly reduced A1C in a dose-dependent manner. Greater A1C reductions were produced by 400 mg

q.i.d. than 200 mg q.i.d. of LX4211 without higher urinary glucose excretion, suggesting a contribution of SGLT1 inhibition. Significant reductions were also seen for body weight and systolic blood pressure. It was concluded that dual inhibition of SGLT1 and SGLT2 with LX4211 produced a significant dose-related improvement in glucose control that was not correlated with glycosuria and was associated with reductions in weight and systolic blood pressure.[14]

**Lipid sensing GPCRs as therapeutic targets**

G-protein-coupled receptors (GPCRs), also known as 7-transmembrane (7-TM) receptors[19], comprise a family of cell-surface receptors that respond to various extracellular stimuli such as light, odorants, neurotransmitters and hormones, and trigger a cascade of intracellular signaling. There are approximately 850 predicted human GPCRs that have specific cell type or tissue-specific expression and are involved in various physiological and clinical processes[20,21]. The function or dysfunction of GPCRs may cause various changes in cellular response, so GPCRs are major drug targets for a wide range of diseases and play a critical role in the development of new medical treatments for humans.[22]

Free fatty acids (FFAs) can act as ligands of several GPCRs, including GPR119, GPR84, GPR120, GPR40 (FFAR1), GPR43 (FFAR2) and GPR41 (FFAR3). Fatty acids are categorized by the length of their aliphatic tails; short-chain fatty acids have less than 6 carbons, medium-chain fatty acids have 6-12 carbons and long-chain fatty acids have 12 or more carbons. Fatty acids can act as signaling molecules that modulate receptor signaling and gene expression.[23,24]

In obesity and type 2 diabetes, elevated levels of plasma FFAs are observed, resulting in lipid accumulation and insulin resistance in target tissues. FFAs exert divergent effects on insulin secretion from beta cells. Acute exposure to FFAs stimulates insulin secretion, whereas chronic exposure impairs insulin secretion. The dual and opposing effects of FFAs on insulin secretion raise the possibility that FFAs contribute to both hyper- and hypo-insulinemia during the development of type 2 diabetes. Thus, GPCRs that recognize fatty acids are of particular interest in the treatment of type 2 diabete.[25]

Previous studies found that GPR120 was highly expressed in adipose tissue, and proinflammatory macrophages. The high expression level of GPR120 in mature adipocytes and macrophages indicates that GPR120 might play an important role in these cell types.[26]

G protein-coupled receptor 120 (GPR120) was initially identified as an orphan receptor through mining the human genome databases. In 2005, GPR120 was deorphanized and shown to be a receptor for long-chain free fatty acids. GPR120 regulates various physiological processes, including gut hormone secretion, islet function, food preference, osteoclastogenesis, anti-inflammation, adipogenesis, and appetite control. Recently, a human genetic study conducted in European populations identified a loss-of-function GPR120 mutation associated with obesity and insulin resistance. Therefore, GPR120, the sensing receptor for long-chain free fatty acids, represents a novel drug target for the treatment of obesity and diabetes[27]. Mo *et al* (2014) reported that GPR119 regulates various physiological processes that improve glucose homeostasis, including glucose-dependent insulin secretion from pancreatic β-cells, gastrointestinal incretin hormone secretion, appetite control, epithelial electrolyte homeostasis, gastric emptying, and β-cell proliferation and cytoprotection. Therefore, GPR119, the sensing receptor for fatty acid metabolites, represents a novel drug target for the treatment of type 2 diabetes mellitus.[28]

Activation of GPR119 leads to insulin release in β-cells by increasing intracellular cAMP. Ha *et al* (2014) identified a novel structural class of small-molecule GPR119 agonists, HD0471042, consisting of substituted a 3-isopropyl-1,2,4-oxadiazol-piperidine derivative with promising potential for the treatment of T2DM. Treatment with HD0471042 for 6 weeks in diet induced obesity mice improved glycemic control and also reduced weight gain in a dose-dependent manner. These data demonstrated that the novel GPR119 agonist, HD0471042, not only effectively controlled glucose levels, but also had an anti-obesity effect, a feature observed with GLP-1. Therefore, HD0471042 represents a new type of anti-diabetes agent with anti-obesity potential for the effective treatment of type 2 diabetes.[29]

**NEW MET (Metformin-delayed release)**

Metformin is the number-one prescribed oral antidiabetic agent in the United States and worldwide, yet its mechanism of action remains poorly understood. Some observations suggested that the glucose-lowering effect of metformin, at least in part, results from a pre-systemic effect on the enteroendocrine L-cells in the small intestine to release gut hormones[7]. Metformin's antihyperglycemic effects have been postulated to result from a wide variety of systemic biochemical interactions including, e.g., suppressing glucose production by the liver, increasing insulin sensitivity, enhancing peripheral glucose uptake

(by phosphorylating GLUT-4 enhancer factor), increasing fatty acid oxidation, and/or decreasing absorption of glucose from the gastrointestinal tract.[30]

Using a delayed-release formulation that escapes absorption in the upper small bowel, 20 healthy subjects and 24 patients with type 2 diabetes were treated with NEW MET (Elcelyx) for 5 days. NEW MET, 500 mg twice daily, was as effective in lowering plasma glucose concentrations as 2,000 mg of metformin immediate release and metformin extended release, despite a 45–68% reduction in plasma metformin exposure. NEW MET, 1,000 mg/day, was 50% more effective in reducing A1C than metformin extended release, 1,000 mg/day, despite plasma metformin levels that were 65% lower. These results demonstrate that NEW MET, which targets the lower bowel, effectively lowers A1C while minimizing metformin exposure. The lower plasma exposure may allow the use of NEW MET in patients with diabetes who have reduced renal function, and the small tablet size will facilitate double and triple combination antidiabetic preparations.[7]

**Thiazolidinediones**

Thiazolidinediones, which developed for the treatment of insulin resistance and type 2 diabetes mellitus, bind and activate peroxisome proliferator-activated receptor-γ (PPARγ), a nuclear receptor that regulates the expression of several genes involved in metabolism. This receptor controls adipocyte differentiation, lipid storage, and insulin sensitization. Besides metabolic activities, thiazolidinediones have effects as diverse as the control of host defense, cell proliferation, and tumorigenesis[31]. The peroxisome proliferator-activated receptors (PPARs) are a group of three nuclear receptor isoforms, PPARγ, PPARα, and PPARδ, encoded by different genes. PPARs are ligand-regulated transcription factors that control gene expression by binding to specific response elements (PPREs) within promoters. PPARs bind as heterodimers with a retinoid X receptor and, upon binding agonist, interact with cofactors such that the rate of transcription initiation is increased. The PPARs play a critical physiological role as lipid sensors and regulators of lipid metabolism.[32]

Thiazolidinedione (TZD) insulin sensitizers have the potential to effectively treat a number of human diseases, however the currently available agents have dose-limiting side effects that are mediated via activation of the transcription factor PPARγ. However, it is now generally accepted that over-activation of PPARγ drives the unwanted and often unacceptable side effects associated with the currently-approved insulin sensitizers, which are PPARγ agonists,

and emerging evidence suggested that the potent anti-diabetic efficacy can be separated from the ability to activate PPARγ.[33]

Recently, Chen *et al*[34] have shown that TZD analogs that do not bind or activate PPARγ at physiologic concentrations have a very similar insulin sensitizing pharmacology as produced by rosiglitazone and pioglitazone in obese rodent models. Moreover, TZDs also exerted insulin-sensitizing effects in isolated hepatocytes that were completely independent of PPARγ as shown by using hepatocytes from liver-specific PPARγ knockout mice. PPARγ-sparing TZDs are now in Phase II clinical trials and a prototype compound has been shown to lower glucose to the same extent as pioglitazone in diabetic patients with reduced side effects associated with activation of PPARγ.[34,35]

Colca *et al* (2013) used a photo-catalyzable drug analog probe and mass spectrometry-based proteomics to identify a previously uncharacterized mitochondrial complex that specifically recognizes TZDs. These studies identify two well-conserved proteins previously known as brain protein 44 (BRP44) and BRP44 Like (BRP44L), which recently have been renamed Mpc2 and Mpc1 to signify their function as a mitochondrial pyruvate carrier complex. Knockdown of Mpc1 or Mpc2 in *Drosophila melanogaster* or pre-incubation with UK5099, an inhibitor of pyruvate transport, blocks the cross linking of mitochondrial membranes by the TZD probe. Knockdown of these proteins in *Drosophila* also led to increased hemolymph glucose and blocked drug action. In isolated brown adipose tissue (BAT) cells, MSDC-0602, a PPARγ-sparing TZD, altered the incorporation of $^{13}$C-labeled carbon from glucose into acetyl CoA. These results identify Mpc1 and Mpc2 as components of the mitochondrial target of TZDs (mTOT) and suggest that understanding the modulation of this complex, which appears to regulate pyruvate entry into the mitochondria, may provide a viable target for insulin sensitizing pharmacology.[36]

Among the thiazolidinedione compounds, troglitazone of Sankyo was first to be approved in Japan and USA. But, following reports of severe liver toxicity in patients taking this drug, the product was withdrawn from the market. Rosiglitazone, developed by SmithKline Beecham and pioglitazone, developed by Takeda/Pfizer are the two thiazolidinedione analogues now in the market. Thiazolidinediones increase insulin sensitivity in fat and muscle tissues and to a lesser extent inhibit hepatic glucose production. As a class, thiazolidinediones have also been shown to alter the lipid profiles in patients with type 2 diabetes. Both the compounds show decrease in triglyceride, although the effect is much significant with Pioglitazone. The effects

on HDL-cholesterol levels have been mostly neutral, while some studies reported an increase in total and LDL-cholesterol levels[37]. Because these agents do not increase insulin secretion, hypoglycemia does not pose a risk when thiazolidinediones are taken as monotherapy. Significant weight gain has been reported with all thiazolidinediones, which is a matter of concern as most of the type 2 patients are already obese. The thiazolidinediones are relatively safe in patients with impaired renal function, but caution should be used in patients with hepatic dysfunction. There are a few reports of deterioration of liver function in such patients after rosiglitazone treatment. The manufacturers recommend these agents not to be prescribed for patients with serum transaminase levels that exceed 2.5 times the upper limit of normal. Mild to moderate edema has been reported in 5 to 7% of patients treated with rosiglitazone and pioglitazone. The increase in plasma volume is of concern in patients with congestive heart failure – particularly those with New York Heart Association class III or IV functional status.[1]

**Insulin secretogogues**

Insulin secretion is reduced in type 2 diabetes. Several novel targets have recently been exploited to develop new drugs, which will increase insulin secretion and thereby glucose utilization. Glucagon like peptide-1 (GLP-1) is secreted by intestinal cells and enhances insulin secretion. Parenteral administration of GLP-1 derivatives normalizes blood glucose in type 2 diabetes, but because of its short half-life it has found little practical application[1]. The incretins are peptide hormones released into the circulation, in response to luminal nutrients, minutes after a meal. In humans, the major incretins are glucagon-like peptide-1 (GLP-1) secreted by the L cells in the ileum and colon and glucose dependent insulinotropic polypeptide (GIP) secreted by the K cells in the duodenum. Hormonal effects on multiple organs are found to be exhibited by both GLP-1 and GIP and stimulate insulin secretion in a glucose-dependent manner along with appetite suppression and delayed gastric emptying. As a result of these combined effects, significant contribution has been made for the control of postprandial glucose resulting in a better glycemic control with relatively low risk of hypoglycemia[38,39]. Nowadays, incretin-based therapies, including GLP-1R agonists and DPP-4 (dipeptidyl peptidase) inhibitors, are becoming widely used as a new class of anti-diabetic drugs that exhibit different mechanisms of action from the conventional antidiabetic drugs[40]. Because DPP-4 is the enzyme responsible for the inactivation of GLP-1, DPP-4 inhibition represents another potential strategy to increase plasma concentration of GLP-1 to enhance the incretin effect. Thus, anti-diabetic properties of these two classes of drugs have

stimulated substantial clinical interest in the potential of incretin-based therapeutic agents as a means to control glucose homeostasis in T2DM patients.[41]

Exenatide, one of the GLP-1R agonists and incretin mimetics, bears a 50% amino acid homology to human GLP-1 and it has a longer half-life in vivo, however, has its side effects including weight loss, nausea and vomiting. It must be injected twice daily. Liraglutide, a once-daily GLP-1 derivative, is also a long-acting GLP-1R agonist that shares 97% sequence identity to human GLP-1(7–37) and has a plasma half-life of 13 hours after subcutaneous administration in contrast to a short half-life of native GLP-1. DPP-4 inhibitors are also available with fewer side effects. ADA/EASD/IDF statement concerning the use of incretin therapy and pancreatic disease was reported in June, 2013.[40]

**Stem cell therapy**

The concept of beta cell replacement therapy has been the ideal for many years, but with the limited number of viable islets and the need for immunosuppression, it has been limited to a very few, and the outcomes have not always been favourable. An early phase study recently commenced using embryonic stem cell-derived cells as replacement therapy in type 1 diabetes (ClinicalTrials.gov identifier: NCT02239354). Furthermore, the push continues for approaches to convert human pluripotent stem cells into beta cells[42,43]. Pancreatic or islet transplantation can provide exogenous insulin independence, but is limited by its intrinsic complications and the scarcity of organ donors[44]. With respect to β-cell replacement strategies, direct delivery of β-cell transcription factors presents an alternative method of achieving a β-cell-like phenotype in autologous tissues. It is clear that the choice of transcription factor for direct delivery has a significant role in determining the success of the cell and gene therapy, as exocrine differentiation and true conversion to a pancreatic phenotype are potential deleterious outcomes. Ideally, an allogeneic cell therapy that is capable of circumventing the autoimmune response would overcome these limitations.[45]

## CONCLUSION

Diabetes is a global major health problem that needs challenging and renewable medications every day as we need to individualize both treatment targets and treatment strategies. Identification of novel targets and techniques for therapeutic intervention will lead to more personalized approaches to treatment and hence to define which medication to be used in whom with regard to benefits and side effects.

**Conflict of interest**

The authors declare that they have no conflict of interest.

**Statement of Human and Animal Rights**

This article does not contain any studies with human or animal subjects performed by the any of the authors.

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