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### Abstract

The first documented case of diabetes mellitus occurred earlier than 4000 BC. Since then, many of the brightest minds in medicine have dedicated their time and effort toward developing treatments that can reverse the course of this deadly disease. As our understanding of the pathogenesis of diabetes increases, so does the availability of treatment options. The fight against diabetes once only had metformin and sulfonylureas as the cornerstone of oral treatment, but now, multiple classes have been added to this armamentarium including thiazolidinediones (TZDs) and dipeptidyl peptidase IV (DPP IV) inhibitors. These therapies provide reasonable durable glycemic control but are unable to arrest the natural progression of diabetes or the eventual need for insulin. By utilizing our growing knowledge on the pathogenesis of diabetes, a number of new therapeutic agents are in development to overcome the shortcomings of current therapies. Promising options on the horizon include sodium-coupled glucose cotransport 2 (SGLT2) inhibitors, Ranolazine, Salicylates, second generation Peroxisome proliferator activator receptor agonists (PPARs), and 11-beta hydroxysteroid dehydrogenase type 1 inhibitors (11-beta HSD1 inhibitors). Various molecules, including some enzymes, are also in development particularly to address beta cell preservation and its sensitivity to glucose, while minimizing hypoglycemia. Most of these new classes of drugs consist of daily administration, simplifying the regimen for patients and likely increasing medication compliance.

This article reviews the new agents that are advancing through clinical trials, their mechanism of actions, glucose lowering effect and possible side effects and limitations

**Keywords:** Type 2 Diabetes; SglT2 Inhibitors; Ranolazine; Salicylates; Second Generation PPARs; 11B-Hsd1 Inhibitors; Glucokinase Activators; Fructose 1; 6 Bisphosphatase Inhibitors

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### Introduction

Diabetes mellitus afflicts approximately 400 million people worldwide and, without any significant change in this trend, by 2030 more than 552 million people will be diabetic [1]. Our current treatment options are able to maintain reasonable glycemic control for a period of time; however, they are unable to stop the progression of disease leading to deteriorating glycemic control over time and subsequent need for increasingly complicated treatment regimens.

The two core defects of type 2 diabetes mellitus (T2DM) are insulin resistance and pancreatic beta cell dysfunction or failure [2]. Insulin resistance appears to be the first and main defect resulting in an increased demand of insulin release from beta cells to normalize glucose levels. Overtime, the beta cells' ability to maintain this level of hyperinsulinemia deteriorates resulting in the hyperglycemia characteristic of T2DM. Insulin resistance is attributed to ectopic lipid deposition in liver, skeletal muscle, and changes in adipose tissue resulting in inflamed tissue leading to the release of a multitude of inflammatory cytokines and decreased release of favorable cytokines and hormones [3,4]. By the time a person develops diabetes, 50-80% of insulin secretory function of beta cells is lost [4]. Additional factors influencing beta cell dysfunction include aging, genetic factors and biochemical abnormalities like lipotoxicity, glucotoxicity, inflammation, amyloid deposition, and reactive oxygen species [5].

Current therapies for T2DM are based on targeting these two core defects. Metformin and sulfonylureas (SUs) are by far the most commonly prescribed medications for T2DM management. Unfortunately, they are unable to arrest the natural course of decline in beta cell function, their effects are not long lasting [6], and they each carry their own side effect profile, with hypoglycemia of particular concern with SU use. Thiazolidinediones (TZDs) improve insulin sensitivity but are notorious for their side effects such as fluid retention, weight gain, fracture, and potential risk of bladder cancer [7,8]. Members of the incretin family include DPP-IV inhibitors and glucagon like peptide (GLP-1) analogs and each have their own limitations. The former have a

limited effect on A1c reduction and a potentially increased risk of pancreatitis, while the latter are injectable and also carry the risk of pancreatitis [9,10].

New therapies, while continuing to address the same two core defects, are being designed to also target various molecular pathways involved in the pathogenesis of T2DM, normalize hyperglycemia, and minimize the complications of T2DM.

### **Sodium-coupled glucose co-transporter 2 inhibitors (SGLT2 inhibitors)**

The kidneys play a significant role in maintaining glucose homeostasis via the filtration and reabsorption of glucose. The reabsorption of glucose predominantly occurs on the brush border membrane of the convoluted segment of the proximal tubule. Glucose enters the tubular cells by a sodium-dependent active carrier-mediated transport process and exits via the basolateral membrane by facilitated diffusion utilizing a sodium-independent glucose transporter (GLUTs) [11]. The sodium-dependent glucose co-transporters are a family of glucose transporters found in the intestinal mucosa of the small intestine (SGLT1) and the proximal tubule of the nephron (SGLT2, predominantly, and SGLT1) [12]. SGLT1 and SGLT2 are members of the SLC5A gene family (also known as the sodium substrate symporter gene family). Twelve of these have been identified in the human genome, and several of these (including SGLT1 and SGLT2) are associated with sodium glucose transport. These transporters use the electrochemical sodium gradient generated by the Na<sup>+</sup>/K<sup>+</sup>-ATPase as the driving force for the symporter activity. SGLT2 is the principal transporter and is responsible for 90% of glucose reabsorption in the kidney. SGLT2 is expressed in the S1 segment of the proximal tubule while SGLT1 is expressed in the S3 segment of proximal tubule and estimated to account for 10% of glucose reabsorption [11,12].

Sodium-coupled glucose co-transporter 2 inhibitors are a class of agents initially derived from phlorizin, a natural component of apple tree bark, that blocks glucose reabsorption in the proximal tubule of the kidney [13].

T2DM patients have increased activity of SGLT2 resulting in increased glucose reabsorption [14] and, therefore, its inhibition is a logical site for intervention. Several oral SGLT2 inhibitors are in different phases of clinical trial. Canagliflozin, Dapagliflozin, Ipragliflozin, Topogliflozin, and Empagliflozin are the most studied drugs in this class. The FDA recently approved Canagliflozin, with the requirement that five post-marketing studies be done including: a study to examine cardiovascular outcomes, a pharmacovigilance program to report the incidences of malignancies, severe pancreatitis, liver abnormalities, adverse events during pregnancy; a study to evaluate bone safety, and two pediatric studies [15]. Dapagliflozin is approved for use in European Union but its approval is delayed in USA due to concerns about an imbalance in breast and bladder cancer events with more cases developing in patients taking the drug [16]. The drop in hemoglobin A1c (HbA1c) with most of these drugs is in the range of 0.7-0.96% with modest weight loss, which is dose dependent, and ranges from 1.35 kg with small dose and 2 kg with maximum tolerable doses [17]. Some side effects of these agents include hypoglycemia, urinary tract infections, genital mycotic infections, salt and volume depletion, and other electrolyte losses such as calcium and magnesium [16,17]. It has not been approved for patients with significant renal impairment and those requiring hemodialysis.

If further data on safety and efficacy continues to be reassuring, SGLT2 inhibitors have a promising future in the management of diabetes.

### **Ranolazine**

Ranolazine, an anti-anginal medication with proven cardiovascular safety profile, acts by inhibiting late sodium current in cardiac tissue [18]. Its mechanism of action for glucose lowering is unknown, but may include augmentation of glucose induced insulin re-lease and a beta cell protective effect [20]. A post-hoc analysis of a study using Ranolazine in T2DM patients revealed that the participants on Ranolazine had a lower HbA1c. The placebo adjusted drop in HbA1c after four months of treatment was 0.42-0.59%. Another notable finding is that the patients on ranolazine did not have a significant difference in hypoglycemic episodes when compared to placebo, and also did not change the incidence of hypoglycemic episodes in patients already on anti-hyperglycemic therapies, including sulfonylureas [19,20].

### **Salicylate derivatives**

The use of salicylates for the treatment of diabetes was proposed over 100 years ago based on the observation that diabetic patients taking salicylates showed improvement in their blood sugar [21]. Our understanding of T2DM as a result of a chronic inflammatory state has reinvigorated the interest in salicylates as a therapeutic option for T2DM. The proposed mechanism of action is via inhibition of NF- $\kappa$ B, which increases the production of proinflammatory cytokines, promoting insulin resistance and down-regulating the insulin-sensitizing adiponectin [21,22]. Some studies have reported evidence that salicylates also directly inhibit adipocyte lipolysis resulting in decreased FFA levels and increased insulin sensitivity. Multiple small clinical trials have been done to evaluate the effect of salicylates on T2DM. Most of these are limited by small sample size and length of study. They also required very high doses of salicylates to achieve the effect, and these were associated with numerous side effects, particularly gastrointestinal bleeding, tinnitus, and hearing loss [23]. Salsalate, a nonacetylated salicylate, is a promising new therapy for T2DM. Salsalate does not affect the COX enzymes, making it a much safer and tolerable option at higher doses than aspirin and other acetylated salicylates. One study examining the benefit of salsalate in T2DM revealed a significant dose-dependent drop in HbA1c, of up to 0.49% with 4g of salsalate. Potential concerns include mild increases in microalbumin to creatinine ratio and in LDL cholesterol [23-25].

### **Peroxisome proliferator activator receptor agonists (PPAR's)**

The PPAR's are a group of nuclear receptors known as ligand-inducible transcription factors, which play diverse roles in regulating growth and metabolism. There are three major isotypes, PPAR- $\alpha$ , - $\gamma$  and - $\delta$ . They form heterodimers with retinoid X receptors (RXR) to either stimulate or repress gene transcription. PPAR- $\alpha$  is mainly expressed in liver, heart, and kidney and plays a role in fatty acid oxidation and lipoprotein metabolism. PPAR- $\gamma$  is expressed in adipose tissue, macrophages, and osteoblasts. It is involved in adipose tissue differentiation and triglyceride synthesis. PPAR- $\delta$  is expressed in skeletal muscle, cardiac muscle, and adipose tissue, where it stimulates fat oxidation [26]. It also is expressed in liver and immune cells where it has a role in reducing hepatic glucose production and inflammation, respectively.

TZDs are an example of PPAR- $\gamma$  agonists, and have had a major impact on reducing insulin resistance to date. Unfortunately, their use has dramatically decreased due to their potential untoward side effects. The first TZD, Troglitazone, was associated with liver toxicity; Rosiglitazone showed increased cardiovascular morbidity, and pioglitazone is linked with a potentially increased risk of bladder cancer and osteoporosis [8]. These side effects appear to be secondary to the non-selectivity of these molecules. Because of their impressive effectiveness in T2DM, there is an ongoing effort to develop second generation of PPAR agonists with more selective action and fewer side effects.

Balaglitazone, a newer partial PPAR- $\gamma$  agonist, has been suggested to be as efficacious in lowering blood glucose with less adverse systemic effects [24,25]. In the BALLET trial, Henriksen et al, compare the effects of balaglitazone to pioglitazone. After 26 weeks, 10mg of balaglitazone lowered HbA1c by 0.99%, compared to -1.11% for 20mg balaglitazone, and -1.22% for pioglitazone 45-mg. This study also showed that balaglitazone was effective in reducing total insulin requirements and increased insulin sensitivity. While there were no statistically significant differences in adverse effects between the two agents, the 10mg dose of balaglitazone showed a trend towards less weight gain, fluid retention, cardiovascular complications, and effects on bone density. Multiple phase III trials are underway in Europe and US to further examine balaglitazone.

Aleglitazar is a member of a new class of dual PPAR- $\gamma$  and - $\beta$  agonists, named glitazars, which is being investigated in phase III trials. Aleglitazar has been reported to improve HbA1c, triglycerides, and HDL in a dose dependent manner [26].

Given these promising results, these agents have great potential for management of T2DM.

## Therapies targeting metabolic enzymes

### *11 $\beta$ Hydroxysteroid dehydrogenase type 1*

#### *(11 $\beta$ -HSD1) inhibitors*

The role of glucocorticoids in adipose tissue metabolism and distribution, lipid and glucose metabolism has long been known, with high levels of glucocorticoids promoting hyperglycemia and insulin resistance, hyperlipidemia, and visceral obesity [27, 28]. 11 $\beta$ -HSD is an enzyme that is involved in the interconversion of cortisol and cortisone and is present in two isoforms, 11 $\beta$ -HSD1 and 11 $\beta$ -HSD2. 11 $\beta$ -HSD1 is predominantly expressed in the liver and adipose tissue and its main function appears to be conversion of cortisone to cortisol [27]. 11 $\beta$ -HSD2 is primarily expressed in the kidneys and colon and acts to inactivate cortisol by converting it to cortisone [27-31].

The incentive to develop 11 $\beta$ -HSD1 inhibitors for the treatment of diabetes has come from our increased understanding of the role between glucocorticoid excess and insulin resistance. The potential benefits of developing compounds that inhibit 11 $\beta$ -HSD1 include weight loss, decreased serum insulin and glucose levels, decreased LDL and TG [27, 30, 31]. However, many compounds that have an inhibitory effect on 11 $\beta$ -HSD1, also inhibit 11 $\beta$ -HSD2. For example, carbenoxolone is a non-selective inhibitor of both 11 $\beta$ -HSD1 and 11 $\beta$ -HSD2 derived from licorice root.

In type 2 diabetics, it was found to improve hepatic insulin sensitivity, but also led to sodium retention, hypertension, and hypokalemia due to its 11 $\beta$ -HSD2 inhibition [29,31]. 11 $\beta$ -HSD1 inhibitory effects have been demonstrated in previously known compounds including rosiglitazone, estrogens, which may help to explain the protective effect they demonstrate in pre-menopausal women, and fibrates [31]. Many new 11 $\beta$ -HSD1 selective compounds are in development, which include INCB13739, an antisense oligonucleotide. In one study, INCB13739 was added to metformin, resulting in an average reduction in HbA1c of 0.6% and up to 1.1kg weight loss. Concerning limitations include interference with the hypothalamic-pituitary-adrenal (HPA) axis leading to mineralocorticoid excess resulting in sodium retention, hypertension, virilization, and menstrual irregularities [30,31]. While the potential utility of these compounds is clear, phase III studies are needed to determine the safety and efficacy of these 11 $\beta$ -HSD1 inhibitors.

#### *Glucokinase activators*

Glucokinase (GK) or hexokinase IV, is an enzyme that catalyzes the addition of phosphate to glucose for further intracellular metabolism. It serves as a glucose sensor in beta cells and initiates the release of insulin from the beta cell. In the liver, this enzyme directs glucose toward glycogen synthesis and lipogenesis. In diabetics, activity of GK is preserved, although decreased due to a lesser number of functional beta cells [32]. Currently, several GK activators are undergoing studies to evaluate their efficacy and safety. This class of molecules targets beta cell core defect in T2DM and liver production of glucose. In a phase I trial, piragliatin resulted in a decrease in fasting and post-prandial glucose in mild diabetics [32]. Concerns include a time-dependent effect on the central nervous system and reproductive system due to the expression of GK in these tissues.

#### *Protein Tyrosine Phosphatase 1B (PTP1B) inhibitors*

This enzyme acts as a negative regulator of insulin signaling by deactivating the insulin receptor. Current data shows its inhibition improves both insulin and leptin action in animals [33]. It may be an option for the treatment of diabetes, but due to its expression in multiple other tissues, other studies are needed to ensure selectivity of these inhibitors to the desired tissues.

#### *Fructose-1,6-bisphosphatase (FBP) inhibitors*

FBP is a rate-limiting enzyme for gluconeogenesis and its inhibition can result in improved blood sugars. A small phase I trial showed improvement in fasting blood sugars in individuals with diabetes [34].

## Conclusion

In the coming years, multiple new therapeutic options will be available to address hyperglycemia and its undesirable side effects. These new therapeutics show great promise for controlling and managing T2DM, but are by no means a cure. The cornerstone of prevention of T2DM lies in healthy lifestyle. Dietary modification and adequate physical activity is the ideal intervention for keeping the threat of diabetes development and its complications at bay. We should continue to emphasize and allocate resources to the education and prevention of T2DM rather than solely depending on treating diabetes after it has occurred

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