

Diabetes and its Complications



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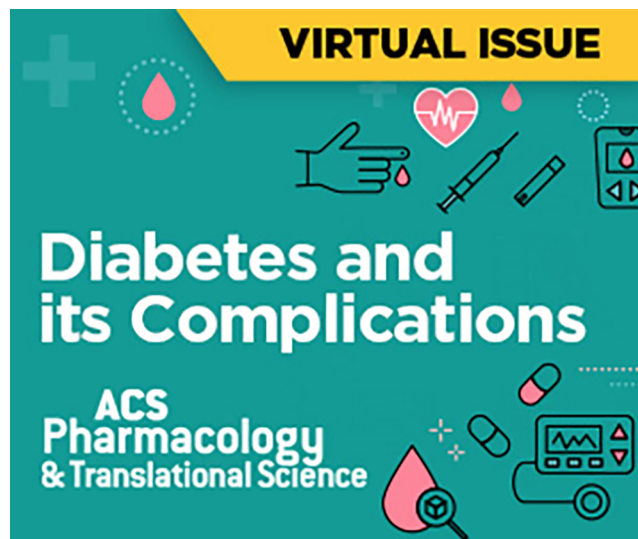
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Diabetes mellitus is defined as “a group of metabolic diseases characterized by hyperglycemia [increased blood glucose levels] resulting from defects in insulin secretion, insulin action, or both”.¹ Insulin deficiency and hyperglycemia result from the destruction of pancreatic beta cells by an autoimmune reaction in type 1 diabetes, or from a reduced response to insulin (insulin resistance) and decreased insulin production by beta cells in type 2 diabetes.¹ Chronic diabetes-related complications affect several organs and include retinopathy, nephropathy, peripheral neuropathy, peripheral arterial disease, and diabetic foot ulcers.¹ The high and rapidly growing prevalence of diabetes presents significant challenges to the health care system. According to the International Diabetes Foundation, an estimated 537 million people were living with diabetes in 2021, and the number of patients is projected to reach 783 million by 2045.² Global diabetes-related health care costs were estimated at 966 billion USD in 2021, and are projected to reach 1,054 billion USD by 2045.²

In view of the high morbidity and financial burden of diabetes, a multitude of initiatives in basic, applied, and clinical research are aimed at identifying new therapeutics for diabetes and its complications and understanding the often complex pharmacology of approved antidiabetic drugs. In this [Virtual Issue](#) of *ACS Pharmacology & Translational Science*, I have curated a selection of the most exciting publications on the pharmacology of approved and investigational treatments of diabetes and its complications.

Pharmacology and Safety of Approved Diabetes Drugs. This [Virtual Issue](#) features articles on the pharmacology and safety of approved diabetes treatments. Lotte Knudsen contributed a Drug Discovery Stories feature on the history of the glucagon-like peptide-1 (GLP-1) analogue liraglutide.³ The article explains how the glucose-lowering activity of GLP-1 was elucidated, and how the rapid elimination of GLP-1 led to the development of liraglutide, a fatty-acid-conjugated derivative of GLP-1 whose glucose-lowering action spans 24 h. Sloop et al. provided a Perspective on polypharmacology in diabetes.⁴ They argued that the therapeutic success of GLP-1 agonists in diabetes, whose glucose-lowering action relies on GLP-1 receptors in different tissues, shall be an inspiration to develop treatments that act on different molecular targets. Indeed, monogenetic approaches often fall short of treating polygenetic diseases such as diabetes, and thus patients often require different drugs for effective disease control. Ala and Ala contributed a seminal Review on one of the oldest and most widely used drugs in diabetes, metformin, in which they described how this drug modulates many aspects of diabetes pathophysiology, including inflammation, cardiovascular and kidney function, and obesity.⁵ Their Review ingeniously



combines information from cell, animal, and clinical studies to explain the multifaceted pharmacology of metformin. Mulka et al. contributed a research article on improving the safety of commercial insulin formulations.⁶ The authors found that after removal of the phenolic preservative, tissue inflammation was reduced without loss of efficacy.

The [Virtual Issue](#) also features studies exploring the effects of antidiabetic drugs on other organs and organ systems. Dhar and co-workers showed that two widely used antidiabetic drugs, canagliflozin and dapagliflozin, reduce oxidative damage and apoptosis of hyperglycemia-treated cardiomyocytes.⁷ With this study, they improved our mechanistic understanding of the cardioprotective effects of these sodium-dependent glucose cotransporter 2 inhibitors. A clinical study by Elfowiris and Banigesh investigated the pharmacology of low-dose angiotensin-converting enzyme inhibitor therapy in diabetes type 2 patients.⁸ Low-dose captopril had a strong effect on several biomarkers of oxidative stress and may be useful to prevent cardiovascular disease in patients with type 2 diabetes. Baruah and co-workers investigated the effects of three sulfonylurea antidiabetic drugs on acetylcholinesterase, an important target in Alzheimer’s disease.⁹ They found a strong inhibitory effect

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of glyburide, which motivates further investigations of this drug or its derivatives in Alzheimer's disease. Riching et al. provided a Review on the utility of approved diabetes treatments in Alzheimer's disease.¹⁰ Starting with the preventive effects of metformin on Alzheimer's disease, they highlighted the many pathophysiologic connections between diabetes and Alzheimer's disease, pointing out the key role of the heart–brain axis and hypertension.¹⁰ Chhanda Charan Danta provided a Viewpoint on the pharmacology of dipeptidyl peptidase-4 inhibitors in diabetic nephropathy and discussed how these inhibitors might decrease the virulence of SARS-CoV2, whose spike protein binds to dipeptidyl peptidase-4.¹¹

Drug Discovery and Translation in Diabetes. This *Virtual Issue* features articles on emerging therapeutic targets, drug discovery studies, and the translation of investigational diabetes treatments. Saed et al. contributed a Review on the role of an emerging therapeutic target, pyruvate dehydrogenase, the rate-limiting enzyme of glucose oxidation, in hepatic glucose oxidation and the development of nonalcoholic fatty liver disease, an important risk factor for insulin resistance and type 2 diabetes.¹² Moreover, Perera and co-workers provided a review on the role of bone morphogenetic proteins in diabetes.¹³ Bone morphogenetic proteins are a subgroup of the transforming growth factor β superfamily and signal via serine/threonine kinase receptors. They are implicated in glucose homeostasis and insulin resistance and play a role in the development of diabetic complications such as diabetic nephropathy, cardiovascular diseases, and diabetic retinopathy.


This *Virtual Issue* also features drug discovery studies that address new targets in diabetes. Wei and co-workers performed a high-throughput screen to identify inhibitors of inositol hexakisphosphate kinase 1, a target implied in insulin sensitivity.¹⁴ Several inhibitors were identified, and their potency was increased with medicinal chemistry structure–activity relationship efforts. Ben Aissa and co-workers developed a drug discovery platform for an emerging target in cholesterol metabolism, ATP-binding cassette transporter A1.¹⁵ This protein plays an important role in cholesterol efflux out of cells and the formation of high-density lipoproteins, and reduced activity is associated with type 2 diabetes, cardiovascular disease, and Alzheimer's disease. The authors developed cell assays to find ATP-binding cassette transporter A1 inducers that upregulate the target protein without inducing unwanted lipogenesis. They validated their hits *in vivo*, where they observed improvements in biomarkers of diabetes without the induction of lipogenesis.

This *Virtual Issue* further includes studies on drug–target interactions of antidiabetic agents. Fang and co-workers contributed a pharmacodynamic study on two natural GLP-1 receptor agonists, native GLP-1 and exendin-4, where they studied receptor binding, endocytosis, and cell signaling of peptide derivatives of these two agonists.¹⁶ The insights from this ligand–receptor interaction study will inform the development of new GLP-1 receptor agonists. Bower and co-workers contributed a pharmacodynamic analysis of amylin and its complex receptor system.¹⁷ The pancreatic peptide hormone amylin is secreted by pancreatic beta cells and involved in appetite regulation and glycemic control. The synthesis of a library of amylin peptide derivatives and binding studies as well as molecular dynamics simulations yielded information on peptide properties that define the selectivity to receptor subtypes.

This *Virtual Issue* also focuses on translation, the process of exploring the therapeutic potential of drug candidates in relevant *in vivo* systems.^{18,19} Chang and co-workers contributed three translational studies on investigational matrix metalloprotease (MMP) treatments for diabetic wounds. Lower extremity wounds are one of the most serious and prevalent complications of diabetes, with a lifetime incidence of 15–25% among patients with diabetes, and associated with low healing and high amputation rates.^{20,21} MMP-9 recently emerged as a high-impact target to improve diabetic wound healing.^{22–26} Chang and co-workers showed that a low-molecular-weight MMP-9 inhibitor accelerated wound healing in infected diabetic mouse wounds alone and in combination with an antibiotic.²⁷ In their efforts to translate this treatment, they also provided *in vitro* metabolism data in different species to select appropriate models for toxicology studies.²⁸ Another study by this group explored the mechanism of action of MMP-8, whose upregulation was associated with improved diabetic wound healing in the past.²⁹ They showed that exogenous administration of recombinant MMP-8 *in vivo* accelerates wound healing by inducing an acute inflammatory reaction and thus jumpstarting the inflammation phase of wound healing.³⁰ With this study, the authors shed light on the mechanism of action of this investigational treatment.

Furthermore, Wu et al. investigated the effects of rosmarinic acid on amylin aggregation in diabetes.³¹ As amylin is co-secreted with insulin, high blood amylin levels and amylin aggregation are common in type 2 diabetes and associated with toxicity in the pancreas, heart, kidney, and brain. The authors showed that rosmarinic acid is a potent inhibitor of amylin aggregation in the pancreas in diabetic rats and has beneficial effects on hyperglycemia. A Review by Fu et al. provided an overview of lipoxin analogues, a new class of anti-inflammatory drugs that promise to reduce diabetes-induced chronic inflammation, and thus reduce inflammation-associated diabetes complications such as kidney and liver disease and atherosclerosis.³²

In conclusion, this *Virtual Issue* of *ACS Pharmacology & Translational Science* features highly exciting research on the pharmacology of diabetes and its complications. These studies use a variety of model systems from cell studies to clinical research to elucidate pharmacologic mechanisms of action of existing diabetes therapeutics, to characterize emerging targets, and to develop new treatments for diabetes.

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■ Notes

Views expressed in this editorial are those of the author and not necessarily the views of the ACS.

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