Metabolic Aspects of Five Commonly Used Non-Insulin Anti-Hyperglycemic Medications in Type 2 Diabetes

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Abstract: Type 2 diabetes is a growing public health challenge while carrying a significant health burden for the patient suffering from it. The worldwide prevalence of diabetes in 2019 was estimated to be 9.3%. Fortunately, a number of drug classes are now available for the medical management of hyperglycemia in this disorder. Metformin and the sulfonylureas are time-tested medications that are effective and inexpensive as first-line medications. The incretin-based therapies, namely the glucagon-like peptide-1 agents and the dipeptyl peptidase-4 inhibitors, offer novel mechanisms of gut hormone and appetite modulation. The former combine weight loss and cardiovascular benefit with glycemic control. The sodium glucose cotransporter-2 inhibitors have a unique glycosuric action that lowers glucose while being of value in congestive heart failure. Almost all these classes of antihyperglcyemic agents can be used in various combinations with one another as well as with different insulin regimens. This article shows the chemical structures and summarizes the mechanistic and therapeutic aspects of the five main classes of noninsulin glucose-lowering medications approved for use in patients with type 2 diabetes.

Keywords: Type 2 diabetes, metformin, sulfonylureas, glucagon-like peptide-1, dipeptyl peptidase-4 inhibitors, sodium glucose transporter-2 inhibitors.

INTRODUCTION

The global prevalence of diabetes increased from 211.2 million in 1990 to 476.0 million (436.6–522.8) in 2017, with a 129.7% increase [1]. Most of this increase has been in type 2 diabetes (T2DM) and is due to detrimental lifestyle changes such as sedentary lifestyle and obesity. The pharmacologic landscape for the treatment of T2DM has undergone a big expansion in the past two decades. To the traditionally available classes of medications have been added new agents that work through different mechanisms of action. The former include metformin and sulfonylureas; while the latter include the dipeptylpeptidase inhibitors, the glucagon-like peptide-1 agonists, and the sodium-glucose co-transporter 2 inhibitors. This brief article describes the *in vivo* metabolic aspects and touches upon the mechanisms of action of these antihyperglycemic agents. A concise summary of the most commonly used five classes of noninsulin antidiabetic medications is shown in Table **1**.

METFORMIN

Metformin is a time-tested, oral medication belonging to the biguanide class. The chemical structure of metformin is shown in Figure **1**. Although its predominant mechanism of action is unclear, it likely reduces plasma glucose through multiple pathways. It is thought to act on the liver to mitigate hepatic glucose output and enhance glucose uptake in the muscle and peripheral tissues through insulin and noninsulin mediated actions. The main route of excretion appears to be the kidney. Excessive accumulation of metformin, especially when coupled with other pathologic states, increases the risk of the life-threatening condition called lactic acidosis. Metformin should not be used in patients with an estimated glomerular filtration rate (eGFR) of <30 mL min^{-1} [1.73 m]$^{-2}$ and only with caution when the eGFR is <45 mL min^{-1} [1.73 m]$^{-2}$ [2]. It should not be used in critical illness, or when volume depletion is present. The most common side-effects are gastrointestinal in nature, such as nausea, vomiting, abdominal bloating, and diarrhea; these symptoms are common and dose-dependent but usually improve with time and may require dose reduction. Metformin use has been associated with low serum vitamin B_{12} concentration. In patients who are deficient in Vitamin B_{12} or have risk factors, therefore, periodic monitoring and supplementation should be considered [3]. Metformin use has been associated with improvement of liver enzymes and hepatic fat content [4].

Metformin may be preferred as the oral medication of choice because it is efficacious, inexpensive, weight-neutral, and carries minimal hypoglycemia risk when used as alone. There is controversy regarding its role in preventing cardiovascular disease (CVD) [5]. It is available as both immediate-release or extended-release formulations that may be administered once or multiple times a day. The different formulations are equally effective with no advantages in side effect

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Table 1: Characteristics of Five Classes of Noninsulin Antidiabetic Medications

Class	Commonly Used Members	Mechanism of Action	Metabolism/ Excretion	Efficacy (expected hemoglobin A1c lowering)	Side Effects	Contra-indications	Cost
Biguanides Figure **1**	Metformin	Reduced hepatic output and increased peripheral uptake of glucose	Renal tubular secretion, excreted unchanged in the urine	1 – 1.5%	Gastro-intestinal (nausea, vomiting, dyspepsia, diarrhea, metallic taste)	Congestive heart failure, metabolic acidosis, diabetic ketoacidosis, renal insufficiency (eGFR<30 mL/min/1.73m2)	Low
Sulfonylureas Figure **2**	Glyburide Glipizide Glimepiride	Enhanced pancreatic beta cell insulin release	Primarily in the liver by the cytochrome P450 (CYP) 2C9 isoenzyme	1.25 – 1.5%	Hypoglycemia, Skin rash/itching, weight gain	History of hypersensitivity to sulfonylureas. Caution in reduced renal or hepatic function	Low
Dipeptyl-peptidase Inhibitors Figure **3**	Sitaglipitin Saxagliptin Linagliptin	Inhibition of the enzyme that degrades endogenous GLP-1	Renal elimination (except linagliptin which is metabolized in the liver)	0.75%	Abdominal pain, nausea, flu-like symptoms, skin rash	History of hypersensitivity reactions. Not to be used in diabetic ketoacidosis or type 1 diabetes mellitus	High
Glucagon-Like Peptide-1 Agonists Figure **4**	Exenatide Liraglutide Dulaglutide Semaglutide	Mimic the actions of the incretin GLP-1	Largely unknown; likely renal route	0.7 – 1.9%	Gastro-intestinal: abdominal pain, nausea, vomiting, diarrhea, constipation	Personal or family history of multiple endocrine neoplasia 2A and 2B, or medullary thyroid cancer	High
Sodium-Glucose co-Transporter 2 Inhibitors Figure **5**	Canagliflozin Dapagliflozin Empagliflozin	Inhibition of the renal enzyme that reabsorbs glucose	Hepatic glucuronidation to inactive metabolites	0.5 – 0.8%	Urinary tract infection, genital yeast infection, upper respiratory tract infection, increased urination	Renal insufficiency (GFR < 45 mL/min/1.73m2)	High

profiles [6]. The starting dose is 500 mg once or twice a day with meals and should be increased slowly as tolerated. The optimal daily dosage is 1,000 mg twice a day, beyond which there is little further advantage in efficacy. The maximum daily dose is 2,550 mg in the U.S. and 3,000 mg in the European Union.

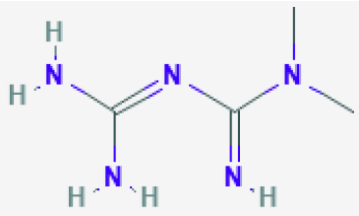

Figure 1: Chemical Structure of Metformin. *National Library of Medicine.* https://pubchem.ncbi.nlm.nih.gov/compound/Metformin#section=Structures, accessed 05-06-2021.

SULFONYLUREAS

Sulfonylureas are oral medications that are inexpensive, widely available, and have high glucose-lowering efficacy [7]. The mechanism by which they lower glucose is by stimulating the release of insulin from pancreatic beta-cells. Because of this, they are hypoglycemic agents in addition to being antihyperglycemic. The molecular structures of some of the most commonly used agents in this class are depicted in Figure **2**. Most of the members in this class are metabolized in the liver, either to inactive metabolites, or to secondary compounds that still retain some hypoglycemic activity. These drugs were studied and showed benefit in the UK Prospective Diabetes Study (UKPDS) [8] and Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) [9] trials. Their glucose lowering lacks durability [7]; thus, their efficacy wanes over time. These agents have a neutral effect on liver fat content [4].

The two major issues associated with sulfonylurea use are weight gain and risk for hypoglycemia [10]. The weight gain associated with sulfonylureas is relatively

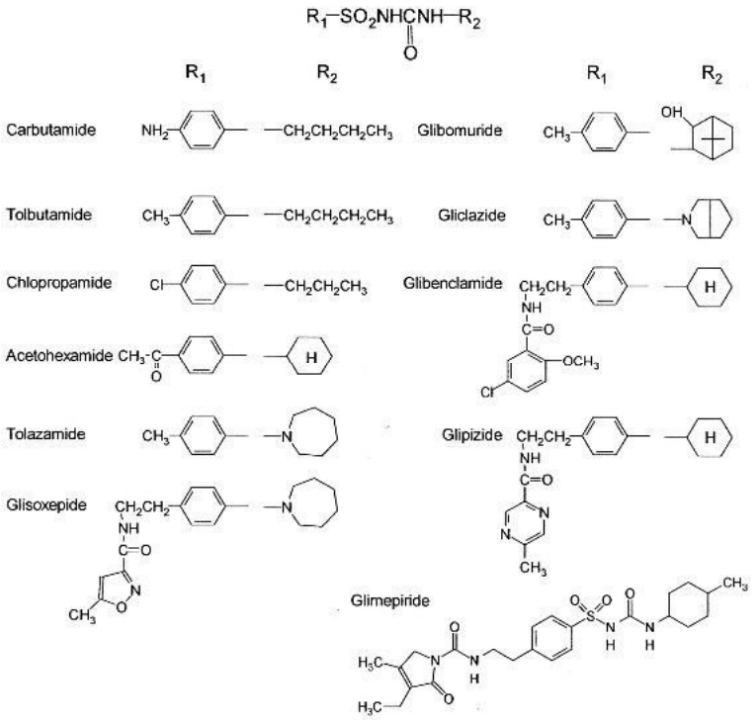

Figure 2: Molecular Structures of the Sulfonylureas. *Diabetes. 2004, 53 (suppl 3) S151-S155. Available at:* 10.2337/diabetes.53.suppl_3.S151https://diabetes.diabetesjournals.org/content/53/suppl_3/S151, accessed 05-06-2021.

modest in large cohort studies. Since newer-generation sulfonylureas appear to confer a lower risk of hypoglycemia and have favorable cost, efficacy, and safety profiles, sulfonylureas remain a reasonable choice among glucose-lowering medications, particularly when cost is an important consideration.

The incidence of severe hypoglycemia is lower than with insulin. The relatively newer agents such as glipizide and glimepiride carry a lower risk for hypoglycemia and are therefore preferred for this reason [11,12]. Patient education and use of low or variable dosing with later generation sulfonylureas may be used to mitigate the risk of hypoglycemia [13]. Greatest caution in this regard is warranted for people at high risk of hypoglycemia, such as older patients and those with CKD.

Adverse cardiovascular outcomes with sulfonylureas in some observational studies have raised concerns, although findings from recent systematic reviews have found no increase in all-cause mortality compared with other active treatments [12].

DIPEPTYLPEPTIDASE-4 INHIBITORS

DPP-4 inhibitors decrease the activity of the enzyme that degrades glucagon-like peptide-1 (GLP-1), the predominant incretin hormone released from the gut post-prandially. In doing so, they increase insulin secretion and reduce glucagon secretion from the liver in a glucose-dependent manner. They have the advantages of oral route, few side effects, and lack of liver fat accumulation and hypoglycemia (except when used in combination with sulfonylureas) [14,15]. There is an association with increased rates of pancreatitis [14] musculoskeletal symptoms [17]. They have moderate glucose-lowering efficacy [18,19]. Since most of the agents in this class are renally excreted, the dose has to be adjusted based on kidney function; linagliptin is the exception, as the kidneys do not appreciably remove it. Cardiovascular outcomes trials (CVOTs) have been conducted with three DPP-4 inhibitors – saxagliptin, alogliptin, and sitagliptin. They have demonstrated cardiovascular safety, but not superiority, in comparison to other agents [20,21]. The molecular structures of three of these agents are shown in Figure **3**.

GLUCAGON-LIKE PEPTIDE-1 AGONISTS

Through their action on specific receptors, GLP-1 receptor agonists, these agents achieve four major actions: they stimulate insulin secretion, reduce glucagon secretion, and improve satiety by slowing gastric emptying, and reducing appetite [22,23]. These effects are achieved in a dose-dependent manner, which minimized the chances of hypoglycemia, except

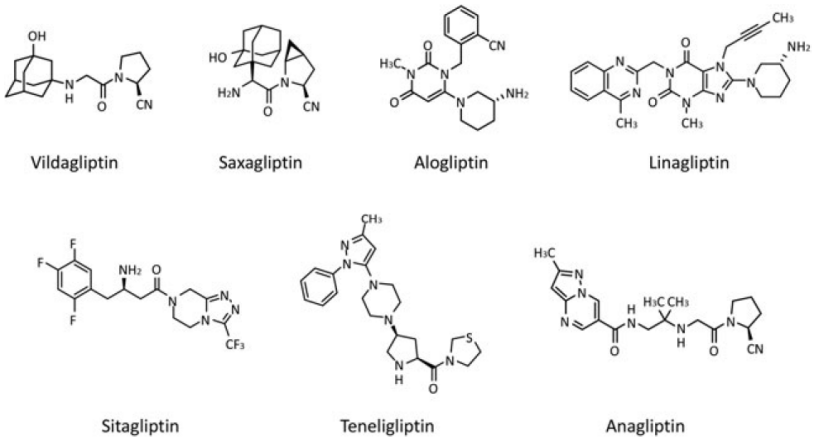

Figure 3: Chemical Structures of the DPP-4 Inhibitors. *Nakamaru et al.* Available at https://onlinelibrary.wiley.com/doi/10.1002/bdd.2003, accessed 05-06-2021.

when used in combination with insulin or sulfonylureas. Since these drugs are inactivated by gastrointestinal enzymes, they cannot be given by mouth and have to be injected subcutaneously.

Figure **4** shows the basic structural framework of the GLP-1 agonists, and variations lead to differences in their duration of action. Their formulation and dosing may affect efficacy, weight reduction, side-effect profile, and actions on the cardiovascular system [23,24]. The long-acting agents that can be given once weekly include dulaglutide, extended-release exenatide, and semaglutide. Exenatide, liraglutide and lixisenatide are administered daily and have greater postprandial

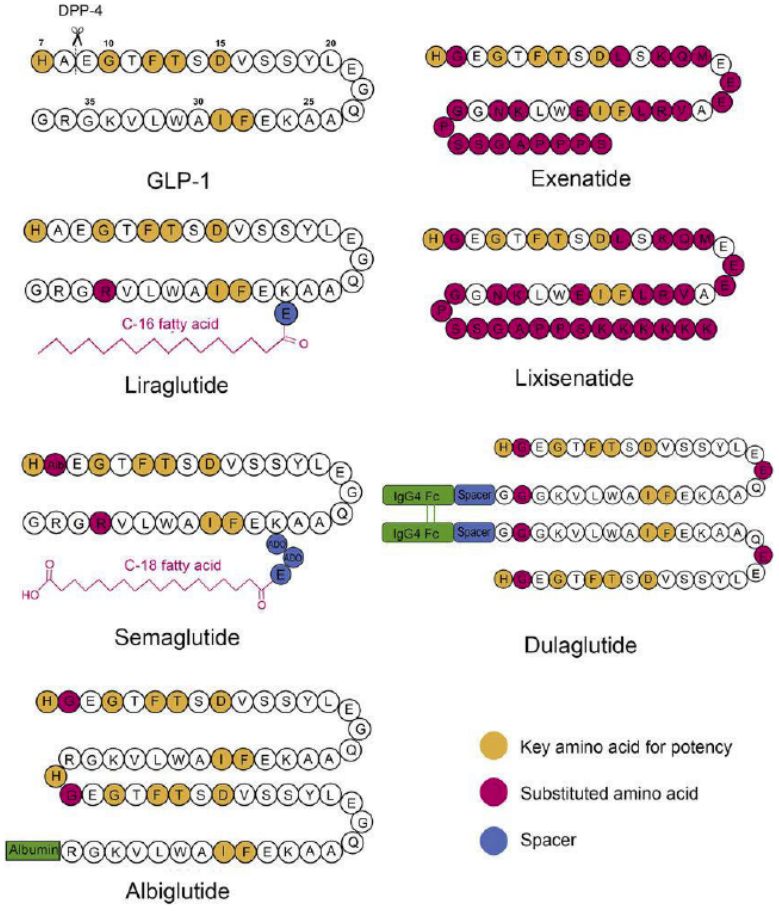

Figure 4: The Chemical Structures and Peptide Sequences of the GLP-1 Agonists. *Yu M, et al.* Available at: https://www.researchgate.net/publication/326447155_Battle_of_GLP-1_delivery_technologies, accessed 05-06-2021.

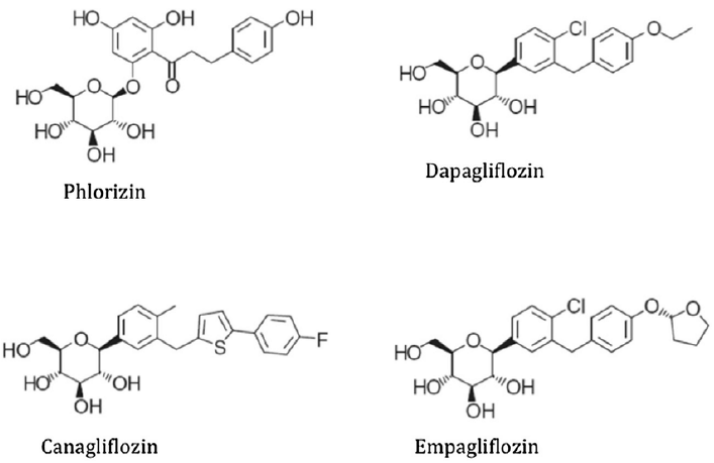

Figure 5: Structures of the common SGLT-2 Inhibitors. Faillie J-L. *Available at:* https://www.researchgate.net/publication/304815132_Pharmacological_aspects_of_the_safety_of_gliflozins, accessed 06-05-2021.

effects. All GLP-1 receptor agonists have the ability to reduce weight, which ranges from about 1.5 kg to 6.0 kg after greater than six months of treatment [25]. Remarkably, there is improvement in nonalcoholic liver disease (NAFLD) by depletion of hepatic fat deposition [4]. The most common side effects of GLP-1 receptor agonists are gastrointestinal in nature. Nausea, vomiting, and diarrhea, though commonly encountered, tend to attenuate with continued use. These agents may increase the hypoglycemic potential of insulin and sulfonylureas when used in combination [26]. There is an association of GLP-1 receptor agonists with increased risk for pancreatitis, pancreatic cancer, and bone loss [27].

SODIUM-GLUCOSE CO-TRANSPORTER 2 INHIBITORS

The main action of the SGLT2 inhibitors is to enhance urinary excretion of glucose by inhibiting the enzyme that reabsorbs it in the collecting tubules of the kidney, thus lowering plasma glucose level [28]. They are safe and efficacious in lowering glucose in the setting of normal renal function, having been approved when eGFR is greater than 45 mL min^{-1} [1.73 $m]^{-2}$ [29]. They do not increase the risk for hypoglycemia and are associated with a reduction in weight, blood pressure, improvement in liver enzymes, and cardiorenal benefits in compromised patients [4, 30]. Their structure is depicted in Figure **5**. Their mechanism of action is responsible for an increased risk of dehydration, orthostatic hypotension, and acute worsening of kidney function. Thus combination with diuretics or antihypertensives can be problematic. The glycosuric action increases the risk for fungal genital infections; vaginitis in women and balanitis in men should be warned against [31]. The SGLT2 inhibitors should be used with caution in patients with insulin deficiency; in such individuals, diabetic ketoacidosis has been reported [32]. An increased risk of fractures and lower-limb amputations has been ascribed to canagliflozin, the original agent in this class [33].

CONCLUDING REMARKS

Clinicians are now equipped with an armamentarium of drugs to treat type 2 diabetes that can be used in various combinations individualized to the patient's situation. Some of these agents have a variety of metabolic benefits on the cardiovascular system that make them attractive to use in certain patient populations. Judicious use of these medications has the potential of helping to ease the therapeutic burden of type 2 diabetes in communities worldwide.

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