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A REVIEW ON HYPOGLYCEMIC AGENTS USED IN NIDDM: MECHANISTIC ASPECTS

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ABSTRACT
Diabetes mellitus is a worldwide rising concern that leads to an increased rate of morbidity, mortality, and health-care costs. Diabetes mellitus is a chronic disease that requires lifelong management to prevent complications such as cardiovascular disease, retinopathy, nephropathy and neuropathy. Oral antidiabetic agents form an important therapeutic strategy in the management of diabetes after lifestyle modification. This review provides an overview of potential antidiabetic drugs, mechanisms, adverse effects and comparison between different clinical, pharmacological, adverse aspects and proved to be beneficial for NIDDM patients as well as several new agents available in the market including dipeptidyl peptidase-4 (DPP4) inhibitors and sodium-glucose cotransporter 2 (SGLT2) inhibitors have been approved for use as monotherapy when diet and exercise are inadequate and also focused on other glucose-lowering agents other than insulin.

KEYWORDS: NIDDM, Hypoglycemic agents, Sulphonyl urea, Mode of action.

INTRODUCTION

In 1979, the National Diabetes Data Group and in 1980 the World Health Organization recognized two major forms of diabetes.[1] Diabetes mellitus (DM) is a complex, chronic disease, yet it is treatable. DM currently affects over 422 million individuals and resulting in increased morbidity, mortality, and health-care costs.[2] One type was termed insulin-dependent diabetes mellitus (IDDM, or type 1 diabetes) and the other non-insulin-dependent diabetes (NIDDM or type 2 diabetes). The prevalence of insulin and non-insulin-dependent diabetes has been largely rising over the past several decades.[3] Previous reports estimated that the number of diabetic patients will reach 552 million by 2030. DM is associated with problems related to cardiovascular, neurological, kidneys besides other complications, and results in effective management planning are of utmost importance.[4]

DM is characterized by disruption of the functioning and active metabolism, due to the lack of insulin or a combination of resistance to insulin and inadequate hormone secretion.[5,6] IDDM arises from pancreatic islet B cell destruction, as a result of an autoimmune process, and these patients are relatively more prone to ketoacidosis and which was known as juvenile diabetes for being more common in children and young adults. NIDDM is the most prevalent form and results from insulin resistance with a defect in compensatory insulin secretion. DM is a serious complication that affects multiple systems in the human body and may result in premature death.[7]

The diagnosis of DM is different from other diseases/conditions and confirmed according to one of the four criteria. Criteria number one involves random blood sugar of 200 mg per deciliter or higher. While criteria two consider fasting blood sugar <100 mg/dl, a patient with fasting blood sugar from 100 to 125 mg/dl is considered prediabetes. However, levels of 126 mg/dl or even higher on two separate tests, indicates diabetes. The third criteria consist of sugar levels >200 mg/dL after a 2 h, 75-g oral glucose tolerance test, and the last criteria involve levels of hemoglobin A1C (HbA1c) >6.5%.[8] Furthermore, it recommends to test all adults beginning at the age of 45 years, irrespective of weight and personality, and to test the conditions of individuals of any age who are overweight or obese, who present a diagnostic symptom, and have at least an additional risk factor for the development of diabetes. The main aim of this study is to outline mechanisms of some antidiabetic drugs used for the treatment of type 2 diabetes, with the hope that this information can be further explored with modern scientific validation approaches to reveal new therapeutic leads for the treatment of diabetes.

MATERIALS AND METHODS

Source of information and search strategy for identifying relevant studies

To ensure a comprehensive research review of the subject, we performed searches using terms such as medical subject headings and key text words, such as "diabetics," "drugs," "mechanism of action" or "hypoglycemic drugs." Thus, the abstracts of published studies with relevant information on the mechanisms, pharmacokinetics, and dynamics of drugs to control diabetes were identified. These terms were used individually and in combination to ensure an extensive literature search. Relevant articles were selected and collated based on the broader objective of the review. This was achieved by searching databases, including PubMed, Google Scholar, SCOPUS, Web of Science, and Embase. From this common methodology discoveries and findings were identified and summarized in this final review. The most common symptoms associated with DM are shown in Fig. 1.

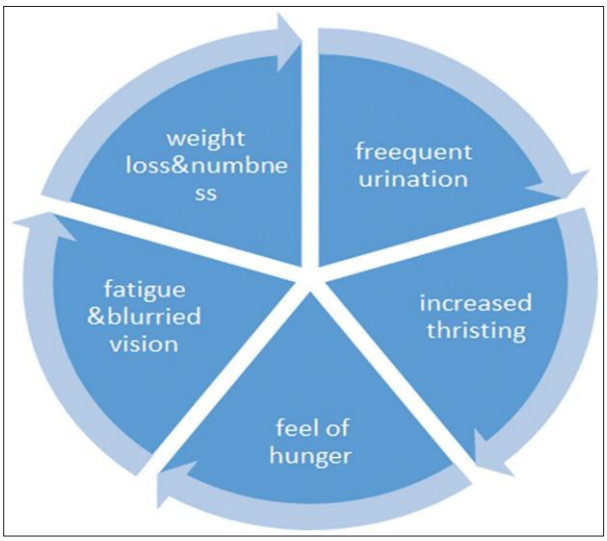

Fig. 1: The major symptoms of diabetes mellitus.

ORAL HYPOGLYCEMIC DRUGS

Sulfonylureas (such as gliclazide, gliclazide, glimepiride, and glyburide)

Sulfonylureas were discovered decades ago by Janbon *et al.*[9], who noticed their ability to control type 2 DM (NIDDM) by different mechanisms.[10] The basic mechanism of sulfonylureas involves the stimulation of the pancreatic islet beta-cells to secrete insulin. An ATP-sensitive potassium channel (K_{ATP} channel) is a type of potassium channel that is gated by intracellular nucleotides, ATP and ADP. ATP-sensitive potassium channels are composed of 6-subunits (sulfonylurea receptor) or SUR subunits. K_{ATP} channels are found in the plasma membrane and subcellular membranes.[11] These drugs bind the adenosine triphosphate (ATP) sensitive potassium channels (K_{ATP}) on the cell membrane of pancreatic beta cells, which depolarizes the cell by preventing K^+ from exiting and thus leads to the opening of voltage-gated Ca^{2+} channels. The increase in intracellular Ca^{2+} leads to increased fusion of insulin granules with the cell membrane, and therefore, augmented secretion of mature insulin. This effect results in amplified responsiveness of β-cells to both glucose and non-glucose secretagogues, resulting in more insulin being released and lower blood glucose concentrations. Due to their mechanisms of action, studies have warned its use in patients with acute myocardial infarction[12]

Even though sulfonylureas and modified aryl sulfonylureas, which have substitutions at the two ends of the molecule, are products of sulfonamides, they do not have no inherent antibacterial activity. Depending on the potency of the sulfonylureas, they are classified as first-or second-generation agents. The sulfonylureas lower blood glucose levels through an increase in secretion of insulin from beta cells. They may also have other extra-pancreatic hypoglycemic actions that are important during prolonged therapy. The second generation sulfonylureas have largely replaced the first generation agents due to its more potency, can be administered in lower doses. First-generation drugs include acetohexamide, chlorpropamide, tolbutamide, and tolazamide. The use of drugs from this class is not currently recommended due to their potential to elicit adverse effects, although these drugs are still available in the United States.[13,14] The common adverse effects of first generation sulphonyl ureas were low blood sugar leads to sweating, dizziness, confusion, or nervousness, excessive hungry, weight gain, skin reactions, upset stomach and Dark-colored urine. However, the second-generation, such as glipizide, gliclazide, and glibenclamide, known as glyburide and glimepiride, is the most commonly used drugs. The sulfonylureas can also be used in combination with other hypoglycemic agents such as metformin, pioglitazone, alpha glucosidase inhibitors, incretin based drugs or insulin. Because of the similarity of mechanism of action, the sulfonylureas not recommended to be used in combination with the metiglinides such as nateglinide and repaglinide. The detailed information about the class drugs and their brand names were given in Table.1

Table 1: The classes of diabetes drugs and their brand names.

Class of drug	(Generic) brand name
Sulfonylureas	Gliclazide Gliclazide Glimepiride Glyburide
Rapid-acting prandial insulin releasers	Prandin nateglinide
Biguanides	Metformin Metformin extended-release
Thiazolidinediones	Pioglitazone, Rosiglitazone
Alpha-glucosidases inhibitor	Acarbose (Glucobay)
Dipeptidyl-peptidase-4 (DPP-4) inhibitors	Linagliptin (Trajenta), Saxagliptin (Onglyza MC), Sitagliptin (Januvia), Alogliptin (Nesina)
Glucagon-like peptide-1 (GLP-1) agonist	Exenatide Exenatide extended-release Liraglutide Dulaglutide Lixisenatide Semaglutide
Sodium glucose cotransporter 2 (SGLT2) inhibitors	Canagliflozin (Invokana) Dapagliflozin (Forxiga) Empagliflozin (Jardiance) Ertugliflozin (Steglatro TM)

All molecules belong to sulfonylurea share similar structural properties. However, second-generation sulfonylureas prescribed in lower doses and are administered once daily due to their high potency and better results have been reported when these drugs were administered with adequate diet and lifestyle changes. Common side effects of the second generation sulfonylureas include headache, dizziness, paresthesias, abdominal discomfort, nausea and weight gain. These agents are also associated with an "antabuse" like response to alcohol (although less likely that with first generation sulfonylureas) and patients should be advised not to drink alcoholic beverages. All sulfonylureas can cause hypoglycemia. The second generation sulfonylureas are all labelled with a special warning about increased risk for cardiovascular mortality.[15,16]

Glyburide, also commonly known as glibenclamide, remains the most popular drug with the brand name of Diabeta and Micronase, and it is available in doses of 1.25, 2.5, and 5 mg. Gliclazide generic drugs with the brand names of Diamicron and Dianorm are available in several countries. Both drugs glyburide and gliclazide have duration of action for up to 12–24 h regarded as an intermediate-acting drug and eliminated through liver and kidney, respectively.[17,18,19]

Similarly, the drug glimepiride, which is very popular with the brand name of Amaryl, is available in doses of 1–4 mg. Combined and fixed doses of glimepiride and thiazolidinediones (TZDs) have also been marketed (rosiglitazone as Avandaryl, and pioglitazone as Duetact). The reported duration of action for glimepiride was longer than 24 h and mainly eliminated through the liver.[20] Another drug called glipizide, also available in the market with the common trade name of Glucotrol, has doses of 5 and 10 mg. It is also available in an extended-release form (Glucotrol XL) of 2.5, 5, and 10 mg. Higher concentrations of the drug should be given in divided doses throughout the day and to a maximum of 40 mg. Fixed combinations of glipizide with metformin are also available in both generic and brand name forms (Metaglip). One of the major drawbacks of sulfonylureas is that they have a high affinity to bind plasma proteins.[21]

Repaglinide, nateglinide

Repaglinide, most commonly available with the name of Prandin, and nateglinide, called with the name of Starlix, are short acting drugs which promote the secretion of insulin and were recently approved for the management of type 2 diabetes.[22] The mechanism of these classes of drugs was related to the that of sulfonylureas; repaglinide and nateglinide exert their efficacy by inhibiting ATP-sensitive potassium channels (KATP channel) in pancreatic β-cells, thus inducing depolarization of β-cell membranes and inflow of Ca^{2+} ions into the cells to stimulate insulin secretion.[23]

Biguanides (metformin, metformin extended-release)

Over decades ago, the use of biguanides has increased around the world, and they are considered as first-line drugs in the management of NIDDM.[8] The primary function of metformin is to decrease the blood glucose concentration, those overweight, and also in those patients whose kidneys function normally. Previous reports revealed that they are safe and effective as monotherapy and in combination with other oral antidiabetic agents and insulin.[24]

Its mechanism of action differs from other classes of oral antihyperglycemic agents. Metformin acts on the liver by decreasing hepatic glucose production; it also decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and consumption.[14] In conjunction with sulfonylureas, the drug metformin does not yield hypoglycemia in patient with NIDDM and does not cause hyperinsulinemia.[25]

The commonly reported side effects of metformin were GI disturbances, including upset stomach, a metallic taste in the mouth, mild anorexia, nausea, and abdominal

discomfort, lactic acidosis, especially in patients with renal insufficiency and soft bowel movements.[26]

Thiazolidinediones (pioglitazone, rosiglitazone)

Thiazilidinediones (TZDs) was introduced in early 1997. They have a strong immunostimulatory effect, to relieve or prevent arthritic symptoms and oncostatic activity.[27] Other studies reported antidiabetic, anti-inflammatory[28], and *in vivo* and *in vitro* anti-cancerogenic effects of these drugs, including in colon, breast, and prostate.[29,30]

TZDs decreases abnormally high blood glucose levels by improving insulin sensitivity. Rosiglitazone and pioglitazone are the only two drugs in this class presently accessible in the United States and by activating PPARs (peroxisome proliferator-activated receptors), a group of nuclear receptors, specific for *PPAR-γ* (PPAR-gamma, PPARG).acts by binding to the nuclear paroxysmal proliferator-activated receptor, subsequently activating genes that encode for proteins involved in the glucose and lipid metabolisms. This interaction leads to a rise in glucose uptake by the skeletal muscle and adipose tissue, a reduction in hepatic glucose output, and finally, an increase in free fatty acid uptake, which in conjunction results in the decrease of glucose and HbA1c levels over the time. Previous data reported that TZD provided lasting glycemic control in diabetes patients.[31] The endogenous ligands for these receptors are free fatty acids (FFAs) and eicosanoids. When activated, the receptor binds to DNA in complex with the retinoid X receptor (RXR), another nuclear receptor, increasing transcription of a number of specific genes. As a result, cells become more dependent on the oxidation of carbohydrates, more specifically glucose, in order to yield energy for other cellular processes. These can be used in both obese and non-obese patients when other treatment options failed. Monotherapy with rosiglitazone has been shown to decrease HbA1c levels by 1.2%–1.5%, compared to placebo after26 weeks of therapy.[32] Similarly, another study reported a reduction of HbA1c levels by ±0.5–1.5%.[10] In addition, the combination of TZDs with metformin and sulfonylureas was considered safe. However, administration of TZDs with insulin was prohibited and it is contraindicated in patients with acute liver disease due to its hepatotoxicity.[10] The most common reported side effects of TZD administration include increased weight (about 1–4 kg over 6–12 months), edema with worsening of cardiac failure, liver toxicity, and anemia.[33]

Alpha-glucosidase inhibitors

Acarbose was the first glucosidase inhibitor discovered in early 1990.[10] Acarbose is an oral antidiabetic drug used for treating NIDDM and show the activity by preventing the digestion of starch and table sugar. The carbohydrates are normally converted into simple sugars by the alpha glucosidase present in the cells lining the intestine. These alpha-glucosidases hydrolyze oligosaccharides, trisaccharides, and disaccharides to glucose and other monosaccharides in the small intestine[10,34], thus facilitating absorption of monosaccharides through the intestine. Previous studies reported that alpha-glucosidase inhibitors also block pancreatic alpha-amylase, which is known to hydrolyze complex carbohydrates into oligosaccharides in the lumen of the small intestine. Inhibition of these enzyme systems reduces the rate of digestion of carbohydrates, which results in reduced absorption of glucose because the carbohydrates are not broken down into glucose molecules. However, the short-term effect of these drugs on diabetic patients is to decrease current blood glucose levels, while the long-term effect is to minimally reduce HbA1c levels.[10,35]

The use of acarbose is prohibited during pregnancy and breastfeeding, and the reported side effects included flatulence, abdominal discomfort, and diarrhea. However, tolerance to the side effects quickly develops. The reported incidence of hypoglycemia can occur when used in combination with sulfonylureas or insulin drugs and products.[10]

Dipeptidyl-peptidase-4 (DPP-4) inhibitors

DPP-4 inhibitors are a class of antidiabetic drugs used in NIDDM. The most common drugs are sitagliptin, saxagliptin, vildagliptin, linagliptin, teneligliptin, and alogliptin. DPP-4 mainly works by blocking the enzyme DPP-4. In 2006, the first DPP-4 inhibitor, sitagliptin, was introduced by Merck pharmaceuticals with the brand name of Januvia and approved by the U.S.F.D.A. This class of drugs represents a novel treatment of diabetes and may be combined with current modalities to improve glycemic control.[36,37]

The major of action of DPP-4 inhibitors is to reduce glucagon and blood glucose levels, by rising incretin levels, such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which prevent glucagon release. Thus, reducing glucagon release increases the secretion of insulin, reduces gastric emptying and decreases blood glucose levels.[38,39] A recent meta-analysis report revealed no favorable effect of DPP-4 inhibitors on all-cause mortality, cardiovascular mortality, myocardial infarction, or stroke.[40]

The most commonly reported that adverse effects were nasopharyngitis, headache, nausea, heart failure[39], acute pancreatitis[41], ulcerative colitis[42], and hypersensitivity to skin reactions. The FDA has issued a warning, which was added to the labels of all medicines in this drug class such as sitagliptin and saxagliptin that they may cause severe and disabling joint pain.[43] However, there was not enough evidence which reveals the risk of rheumatoid arthritis among users of DPP-4 inhibitors.[44]

GLP-1 agonist

GLP-1 as well as GIP secreted by the small intestine in response to food intake. These hormones stimulate

insulin secretion, insulin gene expression, and pancreatic beta-cell growth. In addition, they mediate the incretin effect, which increases insulin secretion subsequent to oral administration of glucose. The GLP-1 molecule is subjected to enzymatic degradation by the DPP-4 (dipeptidyl peptidase) enzyme.[10] The GLP-1 agonists, exenatide, liraglutide, lixisenatide, albiglutide (Tanzeum), dulaglutide,and semaglutide were approved in 2005–2012, 2010, 2016, 2014, 2015[9], and 2017[45] respectively. The patients who recently were diagnosed with NIDDM along with an unbalanced metabolic profile could benefit more from GLP-1 analogs as they stimulate weight loss and improve metabolic dysfunction.

Exendin-4 (exenatide)

Exendin-4, approved in April 2005, belongs to the group of incretin mimetics. This drug was initially isolated from the venom of the Gila monster and has a synthetic version named exenatide. The route of administration is subcutaneously, particularly under the skin of the abdomen, thigh, or arm and should be performed at any time within the 60 min before the first and last meal of the day.[46] Exenatide is used to treat NIDDM as a combination with metformin, biguanide, or a combination of metformin and a sulfonylurea, or TZD, such as pioglitazone.[47] The most common reported side effects of exenatide use were acid or sour stomach, belching, diarrhea, heartburn, indigestion, nausea, and vomiting; therefore, exenatide should not be used by people with severe gastrointestinal disease. Other side effects include dizziness and headache.[48]

Sodium glucose cotransporter 2 (SGLT2) inhibitors

SGLT2 inhibitors are a novel class of FDA-approved medications that have been recently available as monotherapy or in conjunction with other hypoglycemic drugs, including metformin.[49] When these drugs, including canagliflozin, dapagliflozin, and empagliflozin, are combined with healthy food and adequate physical workout, they suppress blood sugar levels in elderly patients with NIDDM.[50]

The main mechanism of SGLT2 inhibitors action is to signal the kidney to eliminate the excess of sugar through the urine. Since their mechanism is glucose-independent; hence, they could be effective in advanced stages of NIDDM when pancreatic β-cell reserves are permanently lost. This class of drugs also stimulates weight loss along with reduction of the blood pressure.[51]

CONCLUSION

Diabetes mellitus is one of the leading causes of several chronic diseases, including renal complications. The disease predominantly affects individuals of all ages irrespective of gender. As the number of patients with NIDDM increases every day, it is becoming a challenge for health-care professionals to treat them. Hence, good knowledge about the drugs used, their chemistry, Pharmacological actions, clinical uses, comparative therapeutic profile and adverse effects very useful in understanding as well as the drugs available in the market in the treatment modalities is of great value.

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CONFLICTS OF INTEREST STATEMENT

The authors declared that they have no conflicts of interest.

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