Diabetes Mellitus: A Comprehensive Overview of Sulfonylureas

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Abstract: Diabetes mellitus is a long-term metabolic disease marked by elevated blood sugar levels, a disease that presents serious risks to global health. The entire spectrum of diabetes mellitus is covered in this review article, including its pathogenesis, division into type I (IDDM), type II (NIDDM), and Gestational DM, and characteristics that set each kind apart. After reviewing the fundamentals of diabetes, the emphasis turns to Su's, a well-known class of antidiabetic medications. In this paper, IR has also been discussed. The review clarifies how molecular alterations affect pharmacological characteristics and therapeutic efficacy by outlining the structural differences among sulfonylureas and their structure-activity relationship. A detailed analysis of the Su's mechanism of action highlights how they block ATP-sensitive potassium channels to stimulate insulin release from pancreatic beta cells. The review also discusses the pharmacokinetics, clinical uses, and possible side effects of Su's. This article aims to improve knowledge of these antidiabetic medicines and guide their appropriate use in clinical practice by incorporating insights into the classification of diabetes, chemistry, and the complex pharmacological profile of sulfonylureas.

Keywords: Diabetes Mellitus, Insulin-dependent diabetes mellitus, Non insulin-dependent diabetes mellitus, Sulfonylureas, Insulin Resistance.

Introduction

Diabetes mellitus (DM) also known as hyperglycemia, is a chronic illness that is caused by a complex interplay of hereditary and/or environmental factors.[1] The frequency of DM has increased dramatically over the last several decades in almost every nation, resulting in a "growing epidemic." The tendency of urbanization, which is seen in almost every country has a significant effect on the prevalence of DM.[2] The incidences of type I and type II diabetes have also grown in children and adolescents, and are estimated to have more than a million cases of type I diabetes.[3] According to estimates from the International Diabetes Federation, there were around 415 million individuals living with diabetes in 2015; by 2040, that number is expected to rise to 640 million.[4]

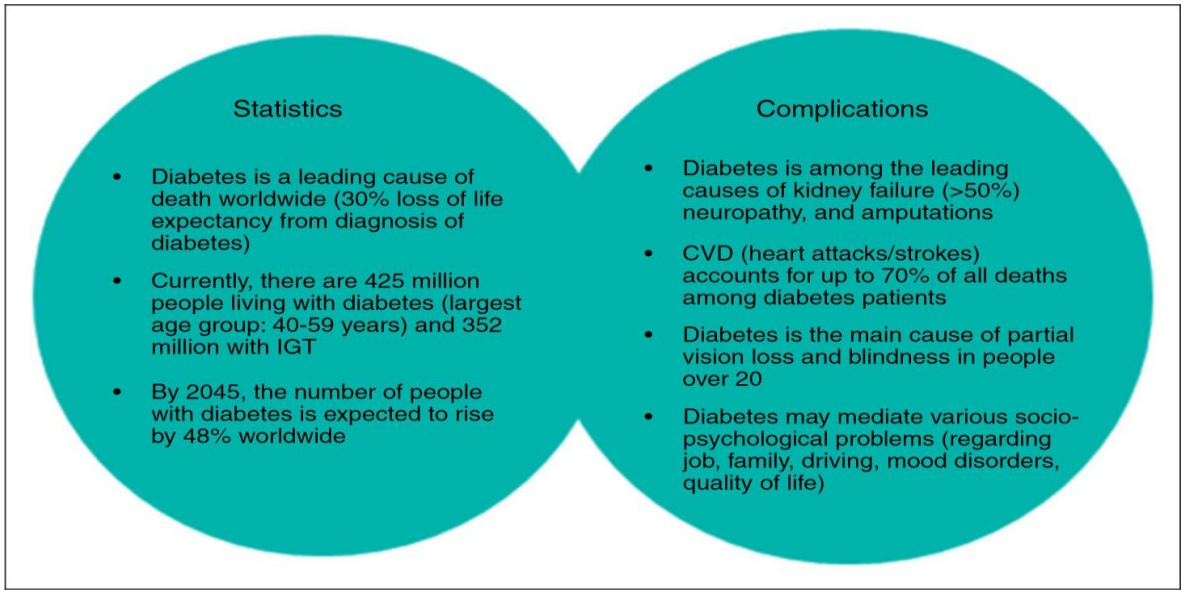

Figure 1. The growing burden of the diabetes epidemic. [5]

Diabetes mellitus is derived from the Latin term mellitus, which means sweet, and the Greek word diabetes, which mean siphon, to pass through. A historical analysis reveals that Apollonius of Memphis first used term "diabetes" about250-300 BC.[6] It is a metabolic disease in which the body fails to make enough insulin or to use it correctly. Insulin isa hormone needed to turn food, sugar, and carbs into energy. Insulin deficiency ultimately results in excessively elevated blood sugar levels and impaired glucose tolerance. Blood sugar level in those who have diabetes remains high.[7] Elevated blood sugar level result in the traditional symptoms of 3 p's, that are polyurea, polydipsia and polyphagia. Three p's are more frequently seen in type I and can grow rapidly. In type II, the three indicators appear more gradually and are essentially undetectable.[8]

The patient must have the following test results in order to establish whether type II diabetes has developed: (a) A plasma glucose level of 126mg/dL or above during fasting. (b) A 200mg/dL or greater plasma glucose level after two hours following a 75-g oral glucose tolerance test (OGTT). (c) In the event of hyperglycemia symptoms, random plasma glucose of 200 mg/dL or above. (d) A minimum hemoglobin A1c level of 6.5 percent. A patient's fasting plasma glucose level of 100mg/dL to 125mg/dL indicates impaired glucose tolerance, often known as prediabetes.

Major Complications of Hyperglycemia

SERIAL NO.	COMPLICATIONS	
	MICROVASCULAR	MACROVASCULAR
1.	Retinopathy	Coronary artery disease
2.	Neuropathy	Cerebrovascular disease
3.	Nephropathy	Peripheral vascular disease

Table 1. Hyperglycemia Complications.[9]

Hemoglobin A1c, or HbA1c, has been included by the American Diabetes Association (ADA) as a diagnostic test for diabetes mellitus (DM) as well as a gauge of the effectiveness of therapies and the management of hyperglycemia (American Diabetes Association, 2010a). According to the Diabetes Control and Complications Trial (DCCT) test, a result of around 48 mmol/moL (6.5%) is thought to be diagnostic of DM (American Diabetes Association, 2010a).[10]

Insulin Resistance

The reduced physiologic response of target tissue to insulin stimulation is known as insulin resistance. Although insulin resistance can develop in any tissue that has insulin receptors, the liver, skeletal muscle, and adipose tissue are the primary contributors.[11] It is the first detectable abnormality in those who may eventually develop type 2 diabetes. There is a clear correlation between obesity and insulin resistance, and obesity rates are rising significantly in the industrialized world.[12]

The main processes are thought to be an early reduction in insulin production and, in many cases, a relative insulin insufficiency linked to peripheral insulin resistance.[13] Insulin resistance increases pathologically as a result of several genotype-lifestyle interactions, the primary ones being sedentary lifestyle and excessive eating. Numerous circulating variables, including circulating hormones, adipokines, plasma lipids, and their signalling pathways, physiologically control insulin sensitivity in target tissue. [14]

Pathophysiology of Diabetes Mellitus

The body's capacity to use insulin levels are linked to the pathophysiology of diabetes. In type I diabetes, there is no insulin at all, but in type II diabetes, the peripheral tissues are resistant to the actions of insulin.[15] The physiological reactions and hyperglycemia are directly correlated. When the brain detects hyperglycemia, it sends the pancreas a message to reduce its impact by nerve impulses.[16] The illness is frequently linked to a number of lifestyle variables, including an unhealthy diet, advanced age, inactivity, obesity, diabetes in the family, early onset of gestational diabetes mellitus in women, and pathological disorders including hypertension, dyslipidemia, and atherosclerosis.[17]

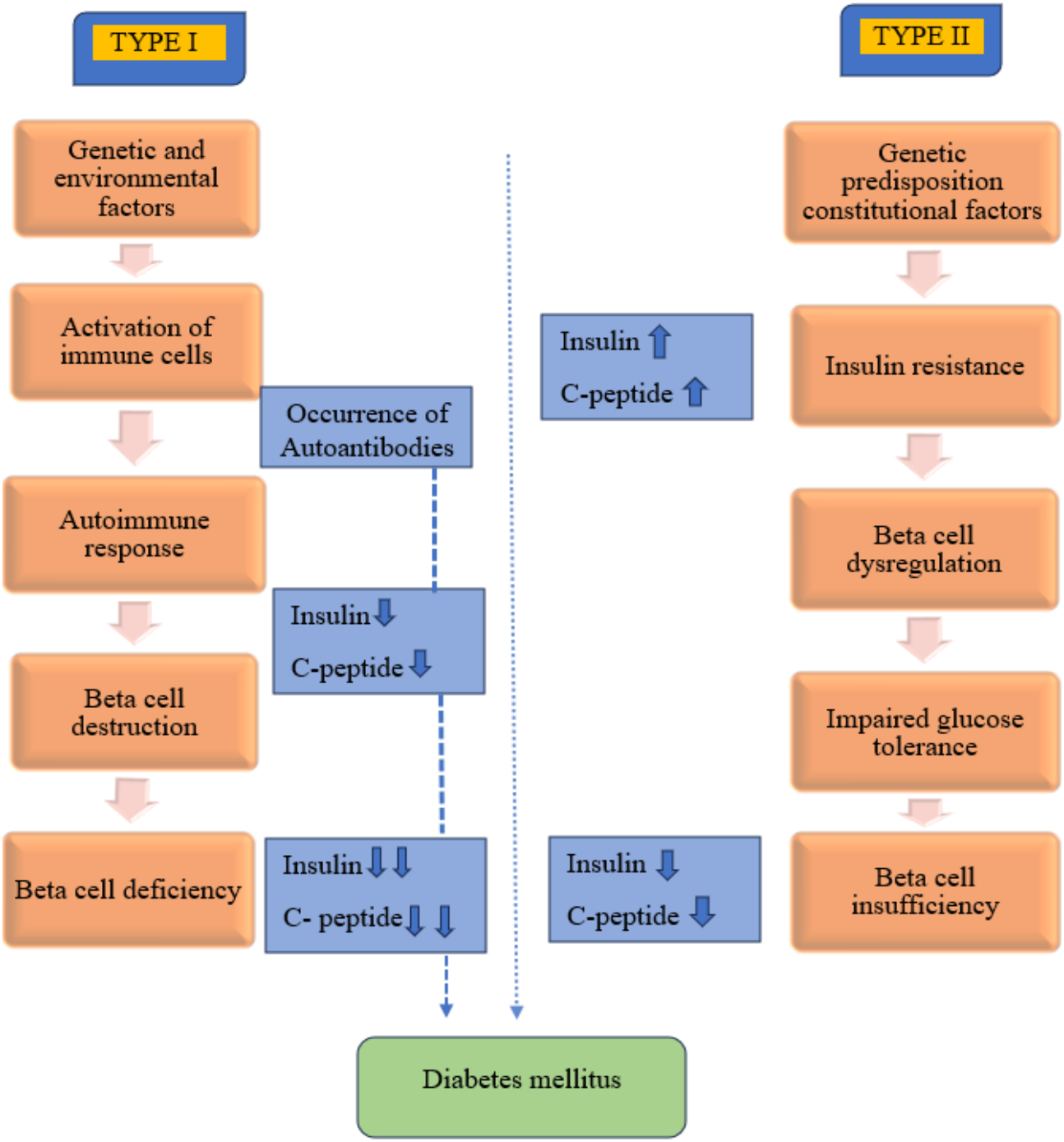

Figure 2. Pathophysiological events leading to type I and type II diabetes.

Types of Diabetes Mellitus

Two broad categories can be used to classify most diabetic patients: type 1 diabetes mellitus, which is characterized by an absolute or nearly absolute deficiency of insulin, and type 2 diabetes mellitus, which is characterized by the presence of insulin resistance with an insufficient increase in insulin secretion to compensate. Furthermore, diabetes that develops in pregnant women is referred to as gestational diabetes.[18]

Type I diabetes mellitus

Type I Diabetes Mellitus, also referred to as juvenile-onset diabetes or insulin-dependent diabetes mellitus (IDDM), represents around 5–10% of all diabetes cases. It's an autoimmune disease where pancreatic β-cells are destroyed by T-cells, leading to insulin insufficiency and eventually hyperglycemia.[19] The primary cause of type 1 diabetes is an autoimmune response that destroys the pancreatic β cells through humoral (B cell) and T-cell mediated inflammation (insulitis). These autoantibodies include those to insulin (IAA), glutamic acid decarboxylase (GAD, GAD65), zinc transporter protein (ZnT8A), protein tyrosine phosphatase (IA2 and IA2β), and islet cell autoantibodies.[20]
There are three phases to T1D development. During the first phase, there are no symptoms and there are ≥2 pancreatic autoantibodies present along with normal glucose tolerance and fasting glucose. To be diagnosed with phase 2, a patient must have dysglycemia (low blood sugar levels between 100 and 125 mg/dL) or impaired glucose tolerance (blood sugar levels between 140 and 199 mg/dL two hours after a 75-gm glucose load), as well as numerous pancreatic autoantibodies. Phase 3 diabetes is characterized by any of the following: fasting glucose levels ≥126 mg/dL, glucose levels ≥200 mg/dL two hours after eating 75 g of glucose during an oral glucose tolerance test, and/or an HbA1c of ≥6.5%. Hyperglycemia is defined as random glucose levels ≥200 mg/dL with clinical symptoms. [21]

T1DM is a condition that can strike at any age, but it usually manifests in adolescents, peaking at puberty. T1DM development is thought to be influenced by a wide range of environmental factors. Among the most frequently mentioned environmental factors include viruses, pollutants, low vitamin intake, early exposure to fruit or cow milk in childhood, obesity, loss in gut bacteria, and gluten.[22]

Type II diabetes mellitus

Type II diabetes mellitus, also known as non-insulin-dependent diabetes mellitus. Insulin resistance, hyperglycemia, and comparatively reduced insulin production are the hallmarks of type 2 diabetes (T2DM), a complicated metabolic illness. Research conducted on adult populations has demonstrated that genetically sensitive people are affected by intricate interplays between environmental, behavioral, and social risk factors leading to type 2 diabetes.[23]

Roughly 90% of instances of diabetes are type II diabetes mellitus. Insulin resistance is the term used to describe the decreased responsiveness to insulin in type 2 diabetes. To maintain glucose homeostasis during this condition, insulin is inefficient and is initially offset by an increase in insulin synthesis. However, over time, insulin production diminishes, leading to Type 2 Diabetes. The majority of people with T2DM are over 45. However, because of increasedrates of obesity, physical inactivity, and energy-dense meals, it is becoming more common among kids, teens, and young adults. [24] Type 2 diabetes rates have been rising recently, and this might be attributed to environmental pollutants. Most people with type 2 diabetes mellitus are obese and have central visceral adiposity. In 1988, type 2 diabetes was initially identified as a part of the metabolic syndrome. It is typified by hyperglycemia, insulin resistance,and relative insulin shortage.[25]

Gestational diabtetes mellitus

The usual pregnancy complication is gestational diabetes mellitus (GDM), a condition in which spontaneous hyperglycemia occurs during pregnancy. According to the most recent (2017) International Diabetes Federation (IDF) estimates, GDM affects approximately 14% of pregnancies worldwide, representing approximately 18 million births annually.[26] Pregnancy-related hypertensive diseases, such as pre-eclampsia, eclampsia, and gestational hypertension, are more common in women with GDM. Glycemic control is the cornerstone of GDM treatment. Lifestyle modifications, such as regular exercise and medical nutrition therapy, are the first line of treatment for GDM.[27]

Moreover, increased amounts of cortisol, progesterone, and estrogen during pregnancy produce changes in the glucose-insulin balance. Hormones and adipokines secreted by the placenta, including human placental growth hormone, human placental lactogen, and tumor necrosis factor (TNF)-α, may be the cause of insulin resistance during pregnancy.

Clinical experience with glyburide treatment of GDM is increasing. When compared with insulin, glyburide had a similar success rate in achieving targeted glucose levels, favorable pregnancy outcomes, and significantly fewer hypoglycemic episodes than insulin. Monitoring blood glucose after meals is recommended in persons with GDM over pre-meal testing, as the risk of macrosomia increases with elevated maternal glucose levels following meals.[27]

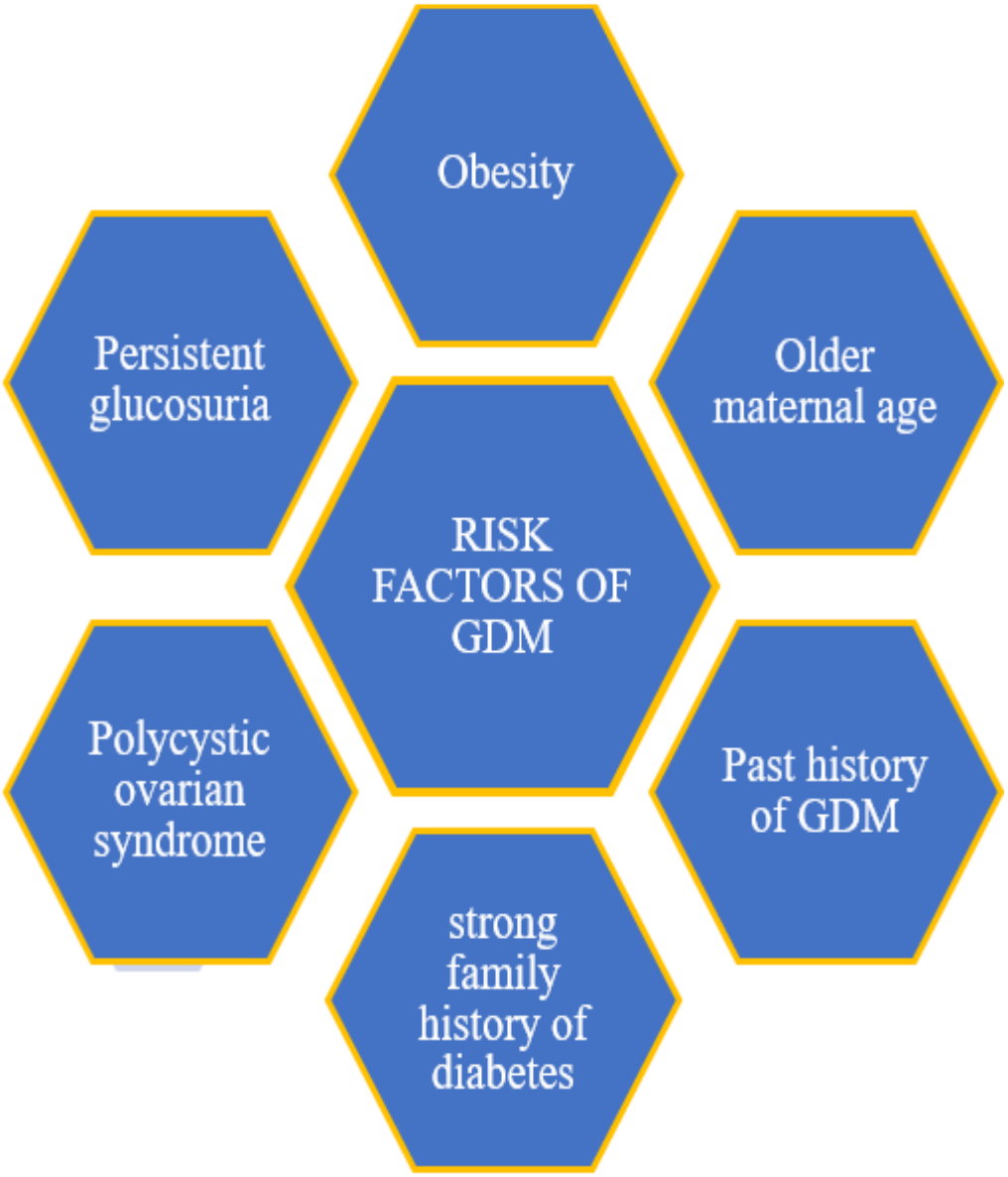

Figure 3. Risk factors of gestational diabetes mellitus.

Anti-diabetic Agents

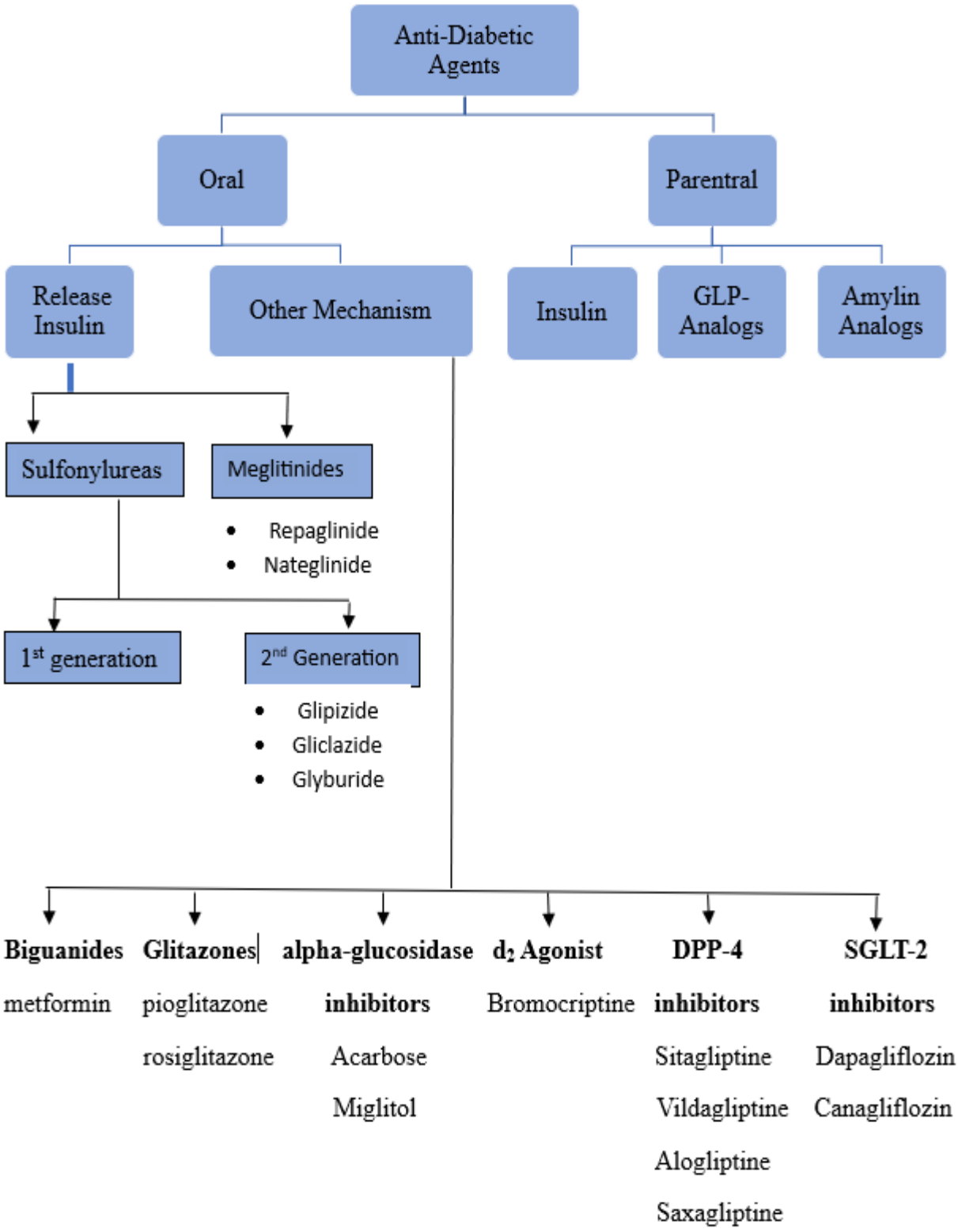

Figure 4. Classification of Anti-diabetic Drugs

Currently available Insulin Secretagogues

Drug	Daily Dose	Duration of Action
Sulfonylureas		
Glyburide	1.25–20 mg, single or two divided	Up to 24
Glipizide	doses 2.5–40 mg, single or two divided doses on an empty stomach	6–12
Glipizide, Extended-release Glimepiride	Up to 20 mg, single dose 1–8 mg, single dose	Up to 24 Up to 24
Non-sulfonylureas		
Repaglinide	4 mg, 2–3 divided doses, 15 min before meals; maximum daily dose 16 mg	3
Nateglinide	60 or 120 mg 3 times/day before meals	1.5

Table 2. Currently available Insulin Secretagogues.[28]

Sulfonylureas

Sulfonylureas are often used in the management of type II diabetes. Patients with diabetes who are not overweight, for whom metformin is contraindicated, or for whom metformin is insufficient to attain appropriate glycemic control, are frequently administered them. Ruiz discovered their hypoglycemic properties for the first time in 1937 while conducting research on sulfa medications. Afterward, in 1942, Jabon verified this effectiveness when he observed that p-amino-sulfonamideisopropylthiodiazole, an antibacterial sulfonamide, produced hypoglycemia action as a side effect when treating typhoid patients.

The first sulfonylurea molecule to be used clinically for the treatment of diabetes was carbutamide, also known as 1-butyl-3-sulfonylurea, in the 1950s. However, it was not used for very long since it negatively affected bone marrow. Tolbutamide, a sulfa medication derivative, was the first sulfonylurea molecule to be used clinically in the treatment of diabetes in 1956 when it was launched in Germany. The German market offered acetohexamide, tolazamide, and chlorpropamide, among other first-generation sulfonylurea drugs. More potent sulfonylurea members, such as glipizide and glyburide, were introduced to the US market in 1984 after being used for more than 10 years in Europe. [29] SUs have been the only option to replace metformin or the most effective adjuvant medication in cases where metformin monotherapy is ineffective over a significant period of time. Newer OADs are available with a number of advantages, such as no weight gain and a very low risk of hypoglycemia. [30]

Second-generation sulfonylurea were developed with increased potency, a faster onset of action, shorter plasma half- lives, and a longer duration of activity. Low blood sugar adverse effects, such as dizziness, sweating, confusion, and anxiety, are common with sulfonylureas. Additional symptoms that may be present include upset stomach, black urine, skin responses, hunger, and weight gain.[31] Sulfonylureas may be an option for diabetic patients who are not overweight, for whom metformin is contraindicated, or for whom metformin is not enough to maintain adequate glycemic control.[32]

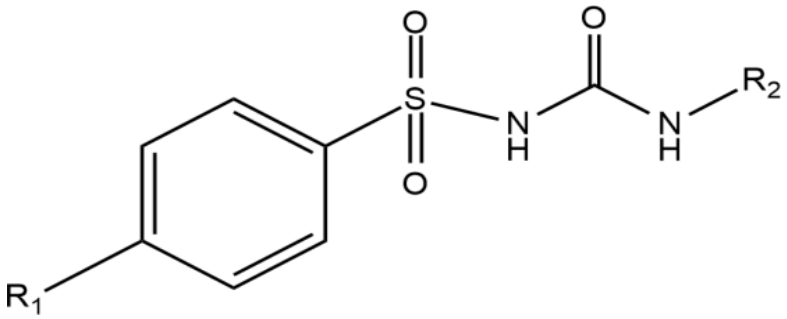

Figure 5. Sulfonylurea Moiety

Sulfonylurea classification

Based on the discovery order, scientists divide these compounds into first, second, and third generations.

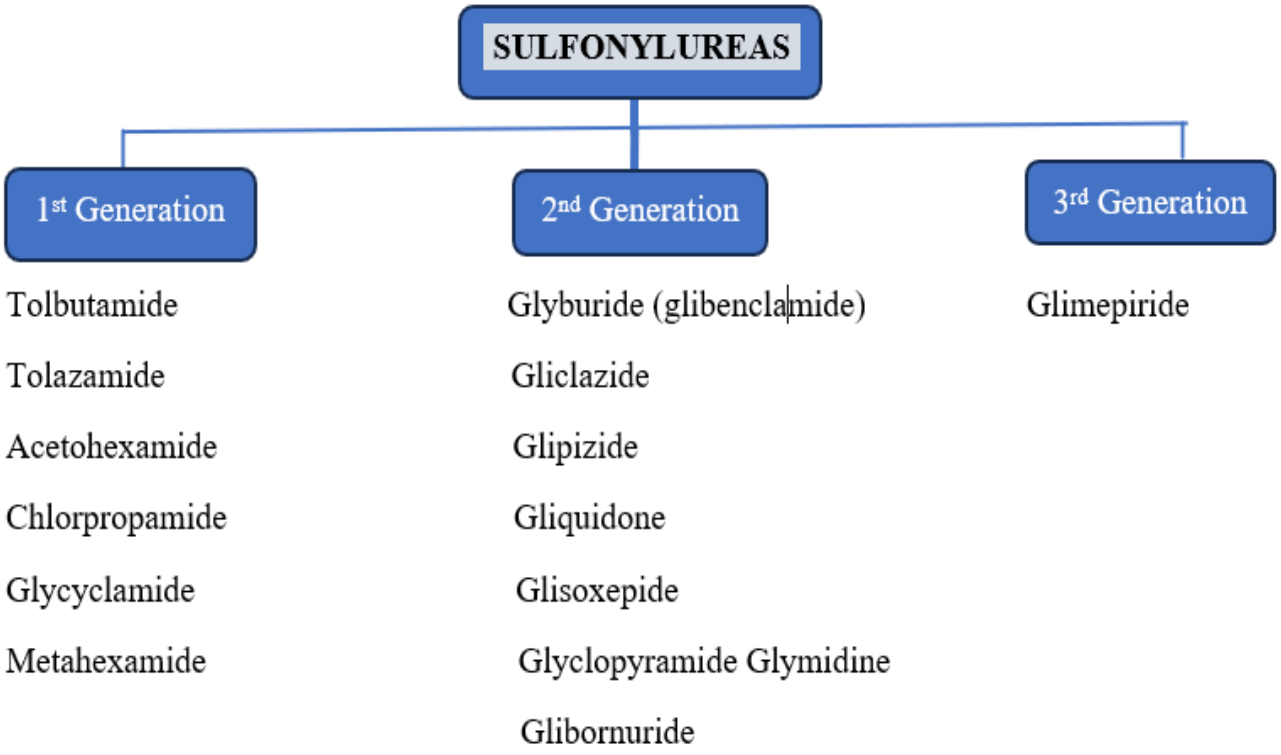

Figure 6. Sulfonylurea classification

Tolbutamide

Tolbutamide is a first-generation sulfonylurea oral hypoglycemic medication used to treat type 2 diabetes mellitus. Because it primarily increases the release of insulin, a situation in which the immune system substantially destroys beta cells, it does not affect type-1 diabetes which has already been established. Patients over 40 and those with diabetes for less than five years had the highest chance of responding. After ten years, only around half of the patients are still receiving adequate sulfonylurea treatment. This is referred to as secondary failure and can result from either beta-cell failure or noncompliance with diet. [33]

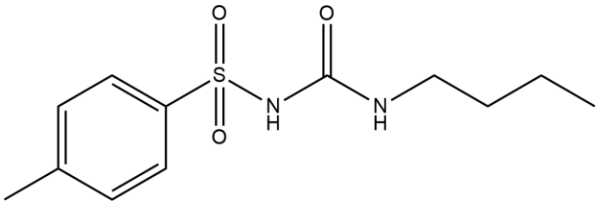

Figure 7. Structure of Tolbutamide.

Tolazamide

Tolazamide is an oral hypoglycemic drug that belongs to the first generation of sulfonylures. Its overall pharmacologyis similar to that of tolbutamide. By attaching to the high-affinity subunit (SUR1) of the beta-cell ATP-sensitive potassium channel (KATP channel), it increases the release of insulin. Binding leads to depolarization of the beta cell,activation of voltage-sensitive Ca2+ channels, influx of Ca2+, blockage of K+ efflux through the KIR 6.2 channel, andrelease of insulin.[34]

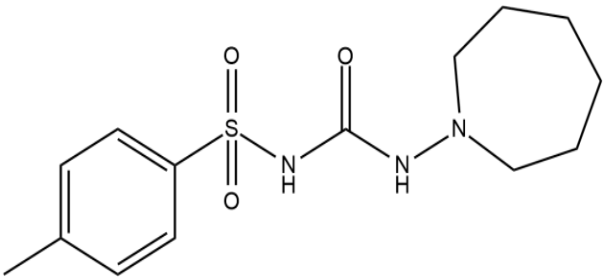

Figure 8. Structure of Tolazamide

Gliclazide

Gliclazide is a second-generation sulfonylurea that reduces blood glucose levels in healthy individuals and those with non-insulin-dependent diabetes mellitus (NIDDM) by treating peripheral insulin resistance and impaired insulin production. It's possible that gliclazide has extrapancreatic actions that raise the sensitivity of peripheral insulin. These effects include decreased hepatic glucose production, increased glucose clearance, and increased skeletal muscle glycogen synthase activity. Insulin-dependent diabetes mellitus, diabetic pre-coma, and coma, diabetes exacerbated by acidosis and ketosis, pregnancy, and the aftermath of severe trauma or illness are among the conditions in which gliclazide should not be used. Individuals who suffer from severe liver or renal failure should not use it.[35]

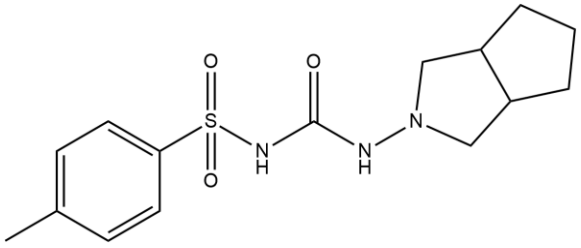

Figure 9. Structure of Gliclazide

Glimepiride

A drug called glimepiride is used to treat and manage type 2 diabetes mellitus. Glimepiride is referred to as a third-generation sulfonylurea due to its superior safety profile and 24-hour half-life. It is an insulin secretagogue that only acts in people who still have some pancreatic beta-cell function, similar to other sulfonylureas. Glimepiride may cause a rise in endogenous insulin secretion, which could lead to hypoglycemia. People with long-term diabetes mellitus may experience hypoglycemic unawareness, a condition in which the patient is oblivious to the autonomic signs of hypoglycemia. Hypoglycemic coma and neuroglycopenia symptoms are possible outcomes of this illness.[36]

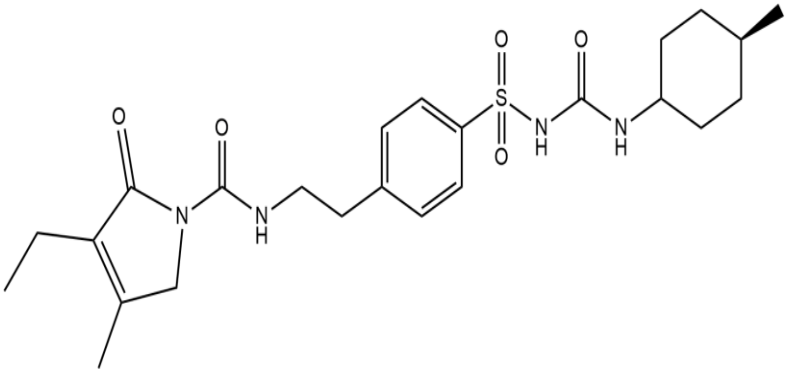

Figure 10. Structure of Glimepiride

Glibenclamide

Glibenclamide, commonly referred to as gliburide, is a second-generation sulfonylurea approved by the Food and Drug Administration (FDA) for treating type 2 diabetes. In their 2023 update to the Standards of Medical Care in Diabetes, the American Diabetes Association (ADA) lists a variety of adjuvant medication choices, including glyburide and other sulfonylureas. This is particularly true for patients seeking highly efficacious medicines with a greater likelihood of assisting them in meeting their glycemic objectives.

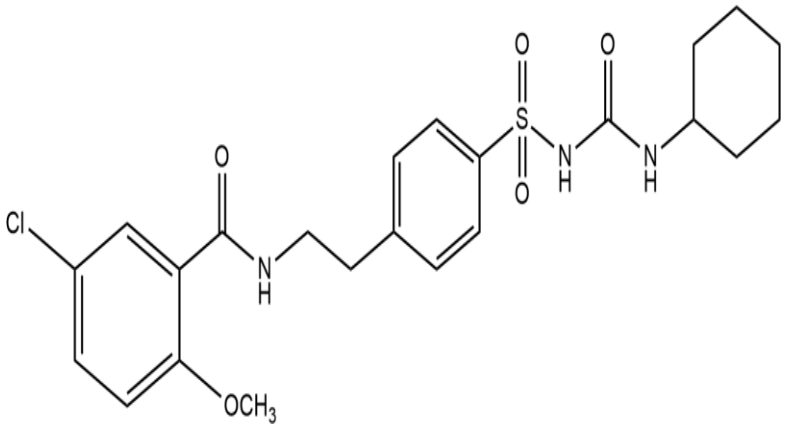

Figure 11. Structure of Glibenclamide (glyburide)

Glyburide is processed by the CYP450 system in the liver and is a substrate of CYP2C9. With a half-life of ten hours, similar to other sulfonylurea class members, glyburide acts by inducing insulin-secreting beta cells in the pancreas.[37] A very small dose is provided since glibenclamide has low dosage activity; for instance, 5 mg of glibenclamide is about equivalent to 1 g of tolbutamide or glymidine, 0.5 g of acetohexamide, or 0.25 g of chlorpropamide or tolazamide.[38] The liver converts glyburide into 4-trans-hydroxy glyburide and 3-cis-hydroxy glyburide; half of these molecules are eliminated in the urine and the other half are eliminated in the bile.[39]

Metabolism and Excretion of Glyburide

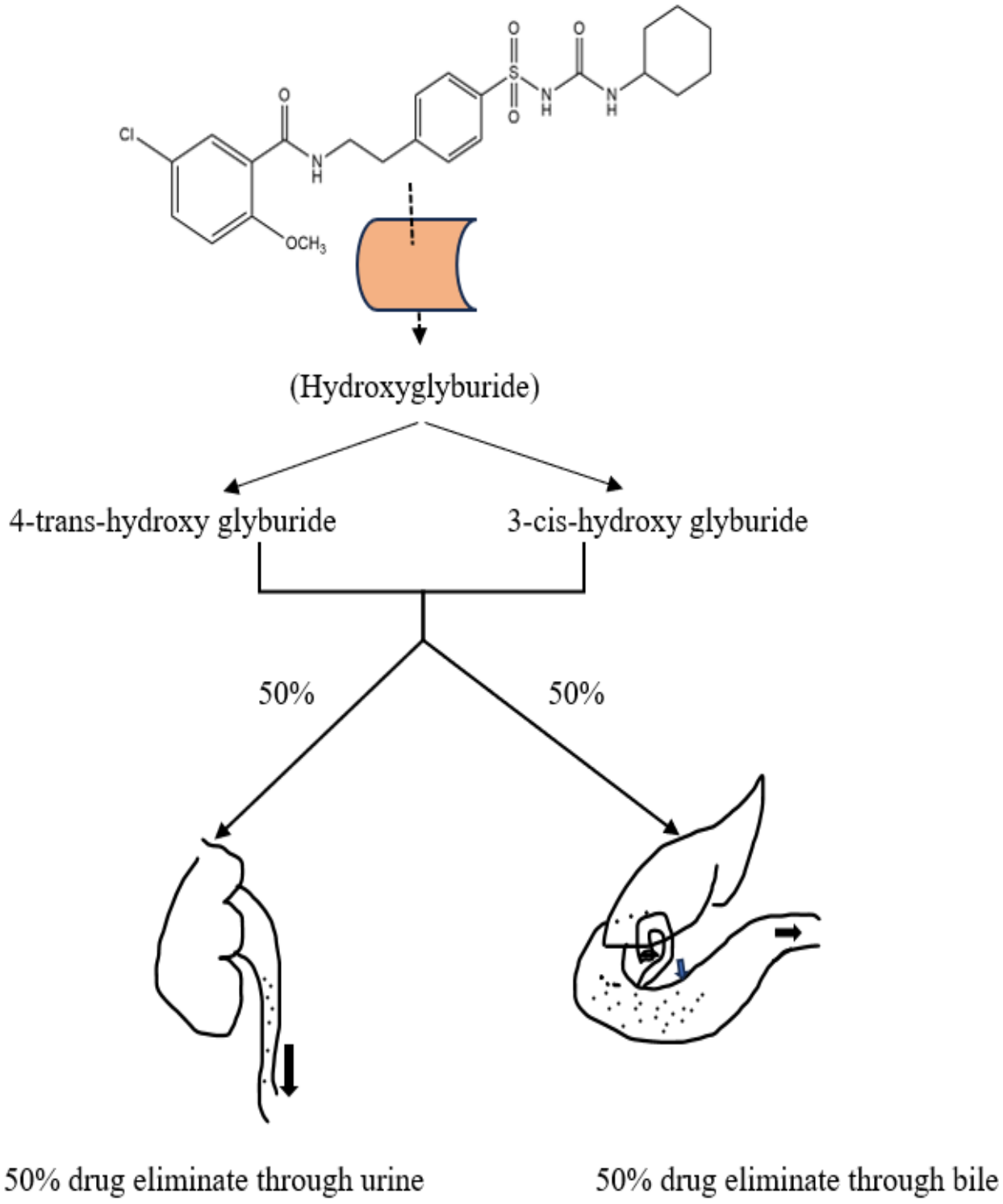

Figure 12. Metabolism of glyburide through the liver and its excretion through urine and bile.

Structure-Activity Relationship

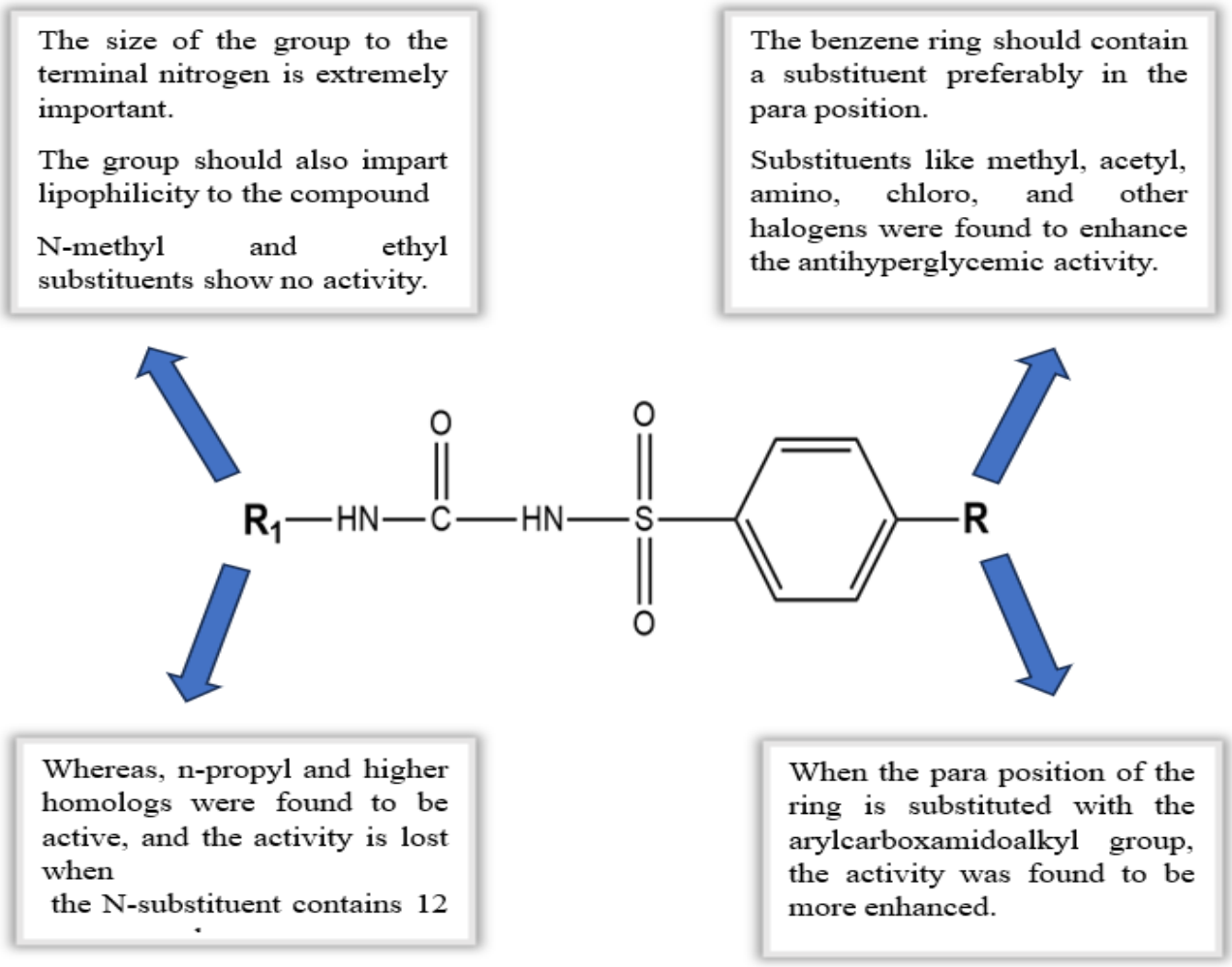

Figure 13. Structure-Activity Relationship of sulfonylurea as Anti-Diabetic.

Synthesis of glibenclamide (glyburide)

Glyburide,1-[4-[2-(5-chloro-2-methoxybenzamido)ethyl]-phenylsulfonyl]-3cyclohexylurea is a second-generation drug which is used to treat moderately severe type II diabetes mellitus without any noticeable microvascular consequences.

It is synthesized from 2-methoxy-5-chlorobenzoic acid chloride, forming an amide by reacting with 2-phenylethylamine. This is subsequently converted to sulfonamide by sulfonylchlorination with chlorosulfonic acid and amination with ammonia. The required glyburide is obtained by reacting the resultant sulfonamide with cyclohexyl isocyanate.[40]

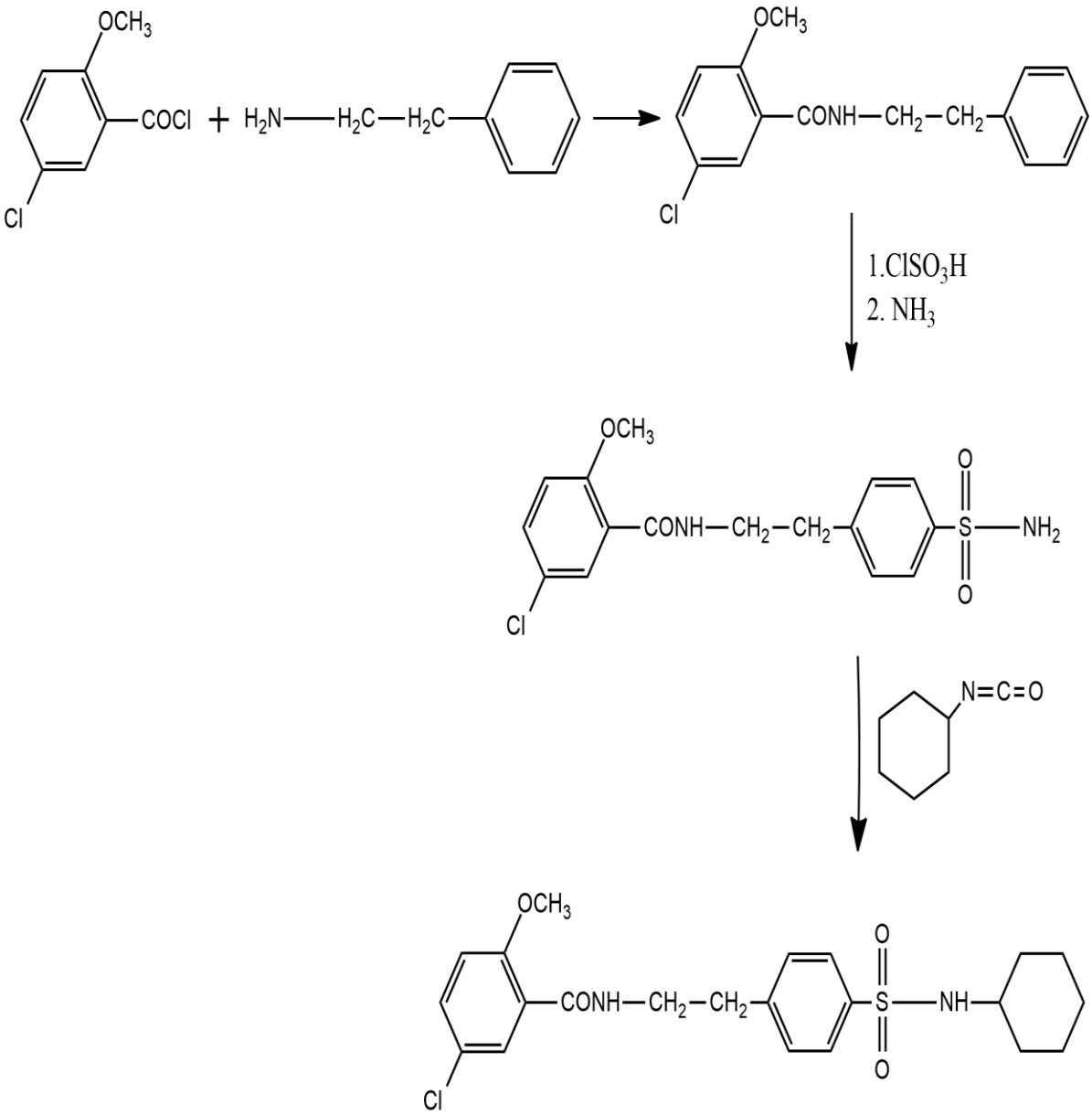

Figure 14. Synthetic Scheme of Glibenclamide

Mechanism of Action

Sulfonylureas bind to and block the potassium channels (K) that are sensitive to ATP in pancreatic beta cells. The beta-cell membrane depolarizes as a result, and potassium outflow decreases. Membrane depolarization causes calcium channels to open, bringing calcium into the cell and raising intracellular calcium levels. This causes the pancreatic beta cells to release insulin.

Insulin is released by sulfonylureas independent of blood glucose levels. K is composed of two proteins: a sulfonylurea receptor (SUR) and Kir6.2, which forms the K channels' pores. Subtypes of SUR include SUR1 and SUR2. The majority of the SUR1 protein is found in the brain and pancreatic beta cells. SUR2 is present in both cardiac muscle (isoform SUR2A) and smooth muscle (isoform SUR2B). Sulfonylureas differ in their affinity for SUR subtype receptors and in how well they inhibit K channels. Unlike the other sulfonylureas, glimepiride has a lower affinity for the heart muscles. It does not generate concerns regarding cardiovascular safety. Sulfonylureas also lower serum glucose levels by decreasing glucagon synthesis, peripheral tissue sensitivity to insulin, and insulin utilization in the liver.[41]

Third-generation SUs like gliclazide MR only have a high affinity for SUR-1, whereas first-generation SUs like tolbutamide, second-generation SUs like glibenclamide, and occasionally third-generation SUs like glimepiride target the SUR-1 present in β cells and, to some extent, the SURs 2A and 2B present in cardiac tissue and smooth muscle, respectively.[42]

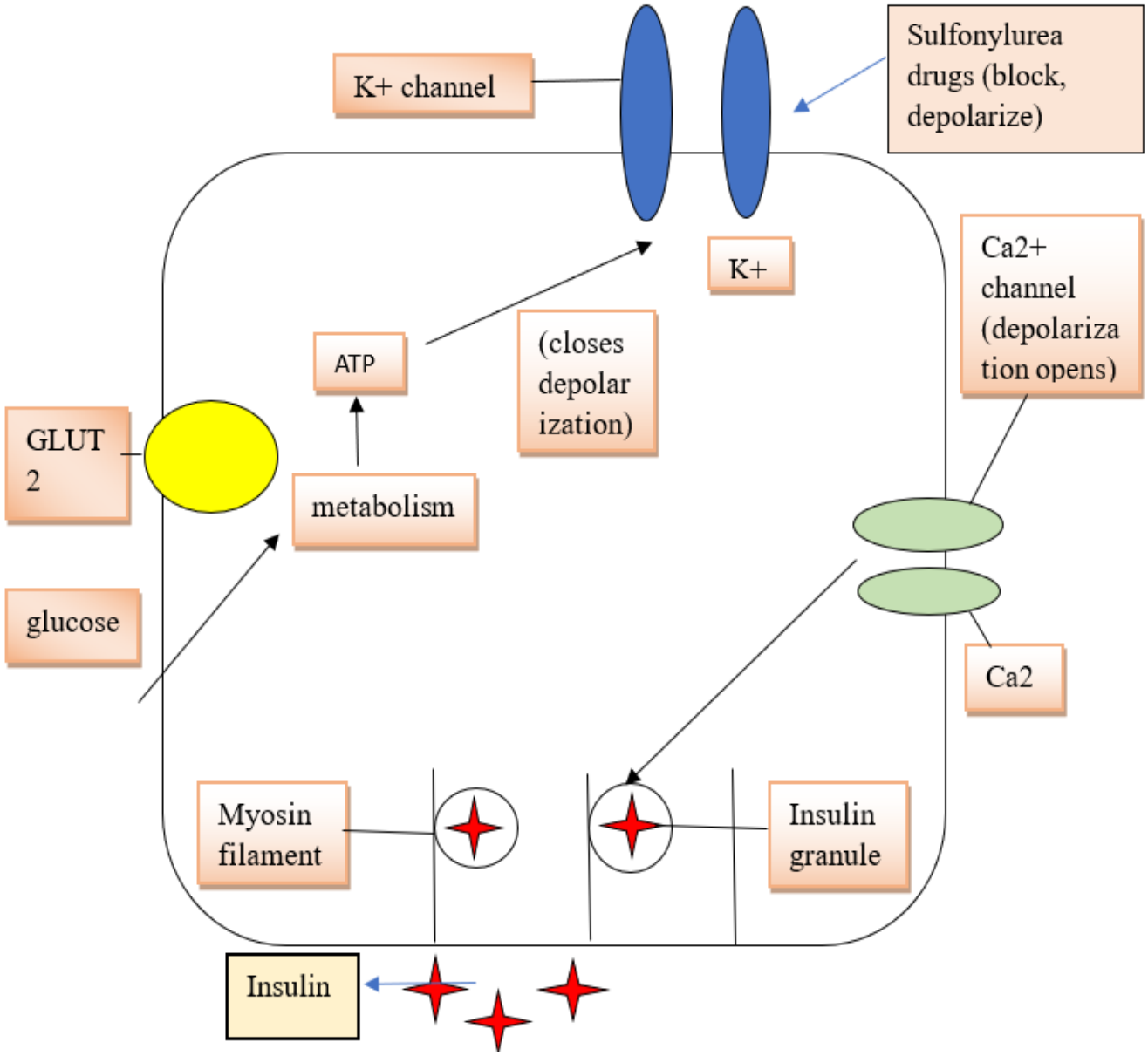

Figure 15. Mechanism of Action of Sulfonylureas

Adverse effects

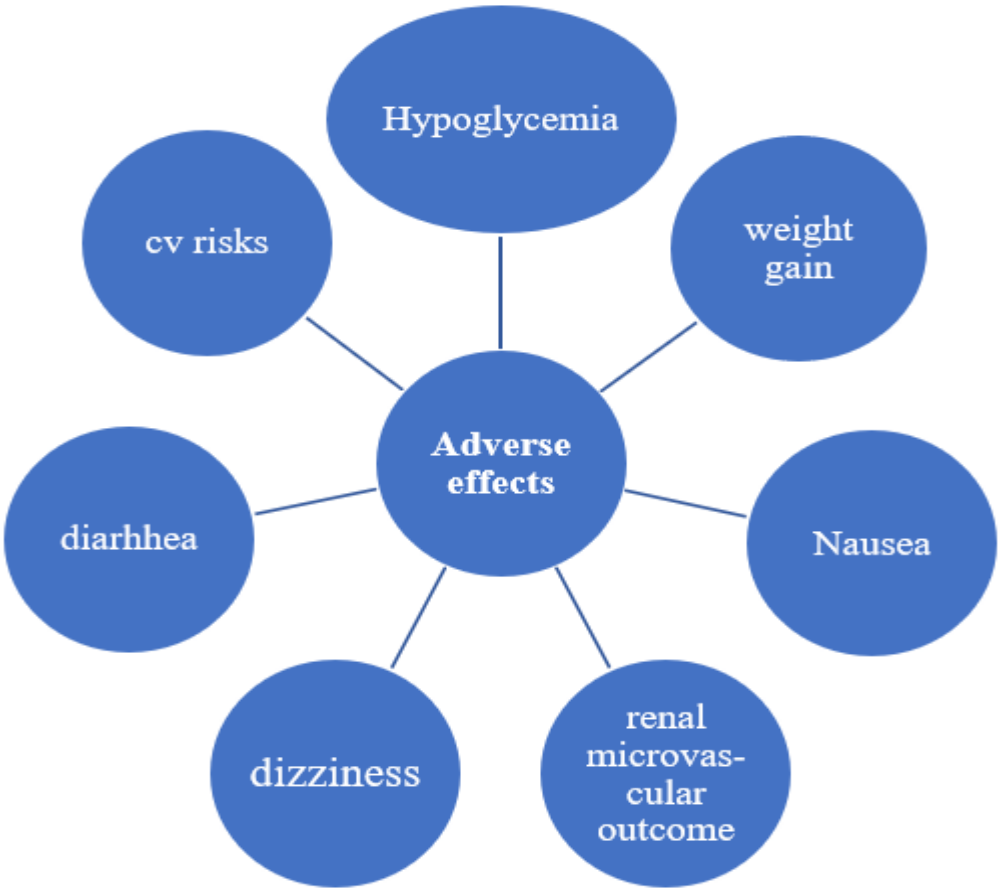

Figure 16. Adverse effects of sulfonylureas**.**

Contraindications

It is not advisable to resume glucose therapy in a patient who has previously had an adverse medication reaction. Those who have previously encountered allergies to drugs in the same class may not experience a negative reaction when taking glyburide.
Moreover, doctors need to be cautious when providing glyburide to hospitalized patients who are underweight, suffer from alcohol addiction, have cardiac and renal dysfunctions, or have gastrointestinal issues.

Drug-drug interaction

Glyburide and bosentan should not be used together. Watch out for potentially harmful drug-drug interactions when patients get concurrent therapy with salicylates, sulfonamides, fibric acid-containing medicines, and warfarin. Other medications inhibiting or promoting CYP2C9 include azole antifungals, carbamazepine, phenobarbital, rifampin, St. John's wort, and dexamethasone. [37]

Conclusion

In conclusion, diabetes mellitus is still a serious public health concern. Its complexity is highlighted by its pathophysiological causes and its several subtypes, including type I, type II, and Gestational DM. Sulfonylureas have shown to be a key component of antidiabetic medication classes, which require a sophisticated understanding for effective management. The categorization of sulfonylureas has been clarified by this review, which also shows how structural differences and structure-activity relationship affect the pharmacological efficacy and safety profiles of these drugs. Their pharmacokinetics can be better understood by thoroughly examining their metabolism and excretion, which is crucial for tailoring treatment plans. The main mechanism by which sulfonylureas produce their hypoglycemic effect

is by inducing insulin secretion in pancreatic beta cells by blocking ATP-sensitive potassium channels.
Sulfonylureas are commonly used and effective, although they are not risk-free. Careful patient selection and monitoring are required due to contraindications and adverse drug reactions (ADRs) such as hypoglycemia, weight gain, and possible cardiovascular problems. To improve patient outcomes, this study emphasizes the significance of weighing the advantages and disadvantages of various treatment options and supports customized approaches. With the development of novel antidiabetic drugs, sulfonylureas' place in the changing therapeutic landscape needs to be regularly reevaluated. Ultimately, this thorough analysis seeks to improve clinical practice by offering a comprehensive grasp of sulfonylureas, leading to more knowledgeable and efficient diabetic care.

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