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Newer Trends in Use Sglt-2 in Diabeties Mellitus

[1]Sangeeta Lodhi, [2nd]Sameer Vishwakarma, *Ritu Soni
[1] *Department of Pharmacy, Adina Institute of Pharmaceutical Sciences (AIPS)*

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ABSTRACT:- Diabetes Mellitus (DM) is a widespread metabolic condition marked by persistent hyperglycemia, impacting millions globally. Conventional therapy methods possess constraints, highlighting the necessity for novel therapeutic solutions. Sodium-glucose cotransporter 2 (SGLT-2) inhibitors have emerged as a potential category of anti-diabetic medications, providing a transformative approach to diabetes management. This review explores contemporary trends in the utilization of SGLT-2 inhibitors, emphasizing their mechanisms, advantages, and prospective applications beyond glycemic regulation. We examine the function of SGLT-2 inhibitors in mitigating cardiovascular risk, safeguarding renal health, and managing weight, along with their prospective use in addressing other metabolic illnesses. Additionally, we examine the most recent studies about the application of SGLT-2 inhibitors in combination therapy, their effectiveness in particular patient demographics, and the current clinical trials. This abstract offers a thorough examination of the present state of SGLT-2 inhibitors in diabetes care, highlighting its future trajectories and potentialities.

KEYWORDS:- Diabetes Mellitus, hyperglycemia, (SGLT-2) inhibitors, future strategies for the management, novel therapeutic solutions.

I. INTRODUCTION

Diabetes Mellitus (DM) is a metabolic disorder characterized by the presence of chronic hyperglycemia accompanied by greater or lesser impairment in the metabolism of carbohydrates, lipids and proteins. DM is probably one of the oldest diseases known to man. It was first reported in Egyptian manuscript about 3000 years ago. In 1936, the distinction between type 1 and type 2 DM was clearly made. Type 2 DM was first described as a component of metabolic syndrome in 1988.

The origin and etiology of DM can vary greatly but always include defects in either insulin secretion or response or in both at some point in the course of disease. Mostly patients with diabetes mellitus have either type1diabetes(which is immune-mediated or idiopathic)Type2 DM (formerly known as non-insulin dependent DM) is the most common form of DM characterized by hyperglycemia, insulin resistance, and relative insulin deficiency Type 2 DM results from interaction between genetic, envionmental and behavioral risk factors. Diabetes also can be related to the gestational hormonal environment, genetic defects, other infections.

II. EPIDEMIOLOGY

The application of epidemiology to the study of DM has provided valuable information on several aspects of this disease such as its natural history, prevalence, incidence, morbidity and mortality in diverse populations around the world. Identification of the cause of the disease and the possible preventive measures that could be instituted to arrest or delay the onset of this disease which has reached epidemic proportions in both the developed and the developing nations.

Unfortunately, the improvement in outcomes for individual patients with diabetes has not resulted in similar improvements from the public health perspective. The worldwide prevalence of diabetes has continued to increase dramatically. Globally, as of 2011, an estimated 366 million people had DM, with type 2 making up about 90% of the cases. The number of people with type 2 DM is increasing in every country with 80% of people with DM living in low- and middle-income countries. Literature search has shown that there are few data available on the prevalence of type 2 DM in Africa as a whole. Studies examining data trends within Africa point to evidence of dramatic increase in prevalence in both rural and urban setting, and affecting both gender proportionally. According to the World Factbook report. in 2008, in Africa the prevalence of diabetes mellitus was 3.2%, and 40,895 persons (2.0%) was in Ethiopia. Although T2DM is widely diagnosed in adults, its frequency has markedly increased in the pediatric age group over the past two decades. Depending on the population studied,

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T2DM now represents8-45% of all new cases of diabetes reported among children and escent. The prevalence of T2DM in the pediatric population is higher among girls than boys, just as it is higher among women than men The mean age of onset of T2DM is 12-16 years; this period coincides with puberty, when a physiologic state of insulin resistance develops. In this physiologic state, T2DM develops only if in adequate beta-cell function is associated with other risk factors (e.g. obesity) . Certain literatures also stated that T1DM is the most common form of diabetes in most part of the world. Wide variations exist between the incidence rates of different populations, incidence is lowest in China (0.1 per 105 per year) and highest in Finland (37 per 105 per year).In most populations girls and boys are equally affected. In general, the incidence increases with age, the incidence peak is at puberty. After the pubertal years, the incidence rate significantly drops in young women, but remains relatively high in young adult males up to the age 29-35 years.

Presently as many as 50% of people with diabetes are undiagnosed. Since therapeutic intervention can reduce complications of the disease, there is a need to detect diabetes early in its course. The risk of developing Type 2 diabetes increases with age, obesity, and lack of physical activity. Its incidence is increasing rapidly, and by 2030 this number is estimated to almost around 552 million [17,5]. Diabetes mellitus occurs throughout the world, but is more common (especially type 2) in the more developed countries, where the majority of patients are aged between 45 and 64 years. The greatest increase in prevalence is, however, expected to occur in Asia and Africa, where most patients will probably be found by 2030 [5] (Table1). It is projected that the latter will equal or even exceed the former in developing nations, thus culminating in a double burden as a result of the current trend of transition from communicable to non-communicable diseases.

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III. CLASSIFICATION OF DIABETES MELLITUS

If any characteristic can define the new intentions for DM classification, it is the intention to consolidate etiological views concerning DM. The old and confusing terms of insulin- dependent (IDDM) or non-insulin-dependent (NIDDM) which were proposed by WHO in 1980 and 1985 have disappeared and the terms of new classification system identifies four types of diabetes mellitus: type 1, type 2, "other specific types" and gestational diabetes [6]. The etiologic classifications of diabetes mellitus are list.

3.1 Type 1diabetes mellitus

Type 1 diabetes mellitus (juvenile diabetes) is characterized by beta cell destruction caused by an automune process, usually leading to absolute insulin deficiency [20]. Type 1 is usually characterized by the presence of anti–glutamic acid decarboxylase, islet cell or insulin antibodies which identify the autoimmune processes that lead to beta cell destruction. Eventually, all type1 diabetic patients will require insulin therapy to maintain normoglycemia.

3.2 Type 2 diabetes mellitus

The relative importance of defects in insulin secretion or in the peripheral action of the hormone in the occurrence of DM2 has been and will continue to be cause for discussion. DM2 comprises 80% to 90% of all cases of DM. Most individuals with Type 2 diabetes exhibitintra-abdominal (visceral) obesity, which is closely related to the presence of insulin resistance. In addition, hypertension and dyslipidemia (high triglyceride and low HDL-cholesterol levels; postprandial hyperlipidemia) often are present in these individuals. This is the most common form of diabetes mellitus and is highly associated with a family history of diabetes, older age, obesity and lack of exercise. It is more common in women, especially women with a history of gestational diabetes, and in Blacks, Hispanics and Native Americans.

3.3 Gestational Diabetes Mellitus (GDM)

Gestational diabetes mellitus is an operational classification (rather than a pathophysiologic condition) identifying women who develop diabetes mellitus during gestation. Women who develop Type 1 diabetes mellitus during pregnancy and women with undiagnosed asymptomatic Type 2 diabetes mellitus that is discovered during pregnancy are classified with Gestational Diabetes Mellitus (GDM). In most women who develop GDM; the disorder has its onset in the third trimester of pregnancy.

3.4 Other specific type (Monogenic diabetes)

Types of diabetes mellitus of various known etiologies are grouped together to form the classification called "Other Specific Types". This group includes persons with genetic defects of

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beta-cell function (this type of diabetes was formerly called MODY or maturity-onset diabetes in youth) or with defects of insulin action; persons with diseases of the exocrine pancreas, such as pancreatic is or cystic fibrosis; persons with dys function associated with other endocrinopathies (e.g.acromegaly); and persons with pancreaticdys function caused by drugs, chemicals or infections and they comprise less than 10% of DM cases.

IV. CLINICAL FEATURES OF DIABETES MELLITUS (TABLE 1.)

Category	Details
Common Symptoms	Weight loss Polyuria Polydipsia Polyphagia
Common Symptoms	Constipation Fatigue Muscle cramps Blurred vision Candidiasis [21]
Microvascular Complications	Retinopathy Nephropathy Neuropathy [22–24]
Macrovascular Complications	Coronary artery disease Heart disease Peripheral vascular disease [25]

V. INSULIN RESISTANCE (TABLE 2.)

Category	Details
Primary Events	- Initial deficit in insulin secretion - Relative insulin deficiency with peripheral insulin resistance [37]
Consequences of Insulin Resistance	- Impaired glucose uptake in muscle and fat - Incomplete suppression of hepatic glucose output - Impaired triglyceride uptake by fat
Compensatory Mechanisms	- Increased insulin secretion by islet cells
Endogenous Glucose Production	- Accelerated in patients with type 2 diabetes or impaired fasting glucose
Hepatic Insulin Resistance	- Considered the main driver of hyperglycemia in early and intermediate disease stages
Plasma Insulin Levels	- Elevated in absolute terms (fasting and post-meal) - Relatively insufficient for the degree of resistance
Glucose Homeostasis	- Controlled through a balance of insulin secretion and sensitivity, difficult to separate in DM2 pathogenesis [20]
Progression	- Leads to impaired glucose tolerance and hyperinsulinemia [36]
Genetics and Inheritance	- Unclear for most of DM2 - **MODY (Maturity Onset Diabetes of the Young):**
MODY Characteristics	- Autosomal dominant inheritance - Often due to glucokinase gene mutations on chromosome 7p [26]
MODY Diagnosis Criteria	- Hyperglycemia before age 25 - No insulin required for at least five years - Negative for islet cell antibodies (ICA)

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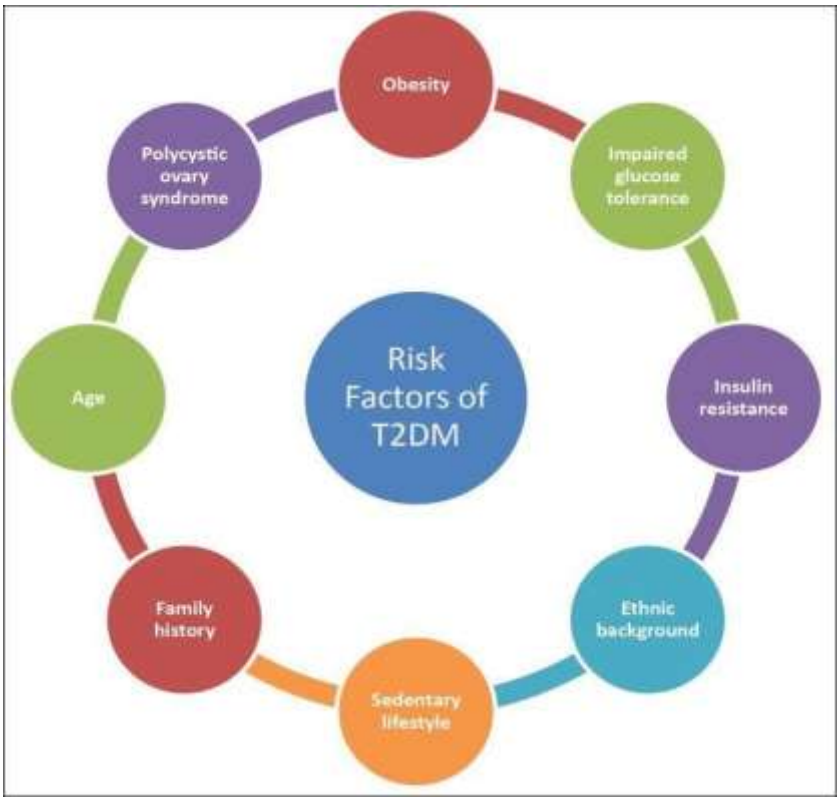

VI. COMPLICATIONS OF DIABETES MELLITUS (TABLE 3.)

Category	Subcategory	Details
1. Acute Complications	1.1 Hypoglycemia	Low blood glucose levels
	1.2 Hyperglycemic Crises	- Diabetic Ketoacidosis (DKA) - Hyperglycemic Hyperosmolar State (HHS)
2. Chronic Complications	2.1 Microvascular Complications	
	2.1.1 Diabetic Retinopathy	Eye damage caused by diabetes
	2.1.2 Diabetic Nephropathy	Kidney damage due to diabetes
	2.1.3 Diabetic Neuropathy	Nerve damage from diabetes
	2.2 Macrovascular Disease	Cardiovascular diseases (heart, brain, peripheral arteries)
3. Other Complications and Associated Conditions	3.1 Impaired Growth and Development	Especially in children and adolescents
	3.2 Associated Autoimmune Conditions	
	3.2.1 Hypothyroidism	Underactive thyroid
	3.2.2 Hyperthyroidism	Overactive thyroid
	3.2.3 Celiac Disease	Autoimmune response to gluten
	3.2.4 Vitiligo	Loss of skin pigmentation
	3.2.5 Primary Adrenal Insufficiency	Also known as Addison's disease
	3.3 Lipodystrophy	- Lipoatrophy (fat loss) - Lipohypertrophy (fat accumulation)
	3.4 Necrobiosis LipoidicaDiabeticorum	Skin disorder seen in diabetes
	3.5 Non-Alcoholic Fatty Liver Disease	Liver fat accumulation not due to alcohol

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	3.6 Infections	Increased risk of bacterial and fungal infections
	3.7 Limited Joint Mobility	Stiff joints, also known as diabetic cheiroarthropathy
	3.8 Edema	Swelling due to fluid retention

VII. DIAGNOSIS OF DIABETES MELLITUS.

The identification of patients with diabetes or pre-diabetes by screening allows for earlier intervention, with potential reductions in future complication rates, although randomized trials are lacking to definitively show benefit. The patient described in the vignette has risk factors (obesity, hypertension, and a family history of diabetes) and should be screened (Table 4) [38-40]. About 25% of patients with type 2 DM already have microvascular complications at the time of diagnosis suggesting that they have had the disease for more than 5 years at the time of diagnosis[41,42].As a result there are different approaches to diagnose diabetes among individuals. The 1997 American Diabetes Association (ADA) recommendations for diagnosis of DM focus on Fasting Plasma Glucose (FPG), while WHO focuses on the Oral Glucose Tolerance Test (OGTT) .

7.1Diagnosis of both types of diabetes

7.1.1 **Random plasma test**

The simplest test and doesn't require fasting before taking the test.

If 200 or more than 200mg/dl of blood glucose it probably indicates diabetes but has to be reconfirmed.

7.1.2 Fasting plasma glucose test:

There should be eight hours fasting before taking this test. Blood glucose more than 126 mg/dl on two or more tests conducted on different days confirms a diabetes diagnosis [43].

Oral glucose tolerance test

When random plasma glucose test is160-200mg/dl and the fasting plasma test is110- 125 mg/dl, then this test is conducted [7].

This blood test evaluates body's response to glucose. This test requires fasting at least eight but not more than 16 hrs.

Fasting glucose level is determined, and then gives 75 gm of glucose, 100 gm for pregnant women. The blood is tested every 30 minutes to one hr for two or three hrs.

This test is normal if your glucose level at two hrs is less than 140 mg/dl. A fasting level of 126 mg/dl or greater and two hour glucose level of 200 mg/dl or Higher confirms a diabetes diagnosis [43].

7.1.3 Glycated proteins

Proteins react spontaneously in blood with glucose to form glycated derivatives. The extent of glycation of proteins is controlled by the concentration of glucose in blood and by the number of reactive amino groups present in the protein that are accessible to glucose for reaction. All proteins with reactive sites can be glycated and the concentrationoftheglycatedproteinsthatcanbemeasuredinbloodisamarkerforthe fluctuation of blood glucose concentrations during a certain period. From a clinical diagnostic point glycated proteins with a longer life time in blood are of interest, since they reflect the exposure of these proteins to glucose for longer periods.

7.1.4 Glycated haemoglobin

The life span of hemoglobin in vivo is 90 to120 days. During this time glycated hemoglobin A forms, being the ketoamine compound formed by combination of hemoglobin A and glucose. Several subfractions of glycated hemoglobin have been isolated. Of these, glycated hemoglobin A fraction HbA1c is of most interest serving as a retrospective indicator of the average glucose Concentration. HbA1c is recommended as an essential indicator for the monitoring of blood glucose control. The blood HbA1c≥ 6.5% is considered as diabetes.

VIII. SGLT 2 INHIBITORS.

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors are anti hyperglycemic agents acting on the SGLT-2 proteins expressed in the proximal convoluted tubules. These drugs exert their effect by preventing the reabsorption of filtered glucose from the tubular lumen. To date, there are four SGLT-2 inhibitors: canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin that are approved by Food Drug Administration (FDA) for their use in adults. The indications for use vary per agent, but all four agents are approved for use in adults with type 2 diabetes mellitus (DM) to improve blood sugar control adjunct to diet and exercise. If

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you have and you've already tried other treatments, your doctor may suggest you take SGLT2 inhibitors. They keep your kidneys from absorbing as much blood sugar to help you get rid of it.

8.1 Pharmacokinetics: Absorption: SGLT inhibitors are well absorbed from the gastrointestinal tract. The effect of food on SGLT2 pharmacokinetics is not statistically significant; ertugliflozin, dapagliflozin, and empagliflozin may be administered with or without food. However, to reduce postprandial plasma glucose elevation due to delayed intestinal glucose absorption, it is recommended that SGLT2 inhibitors should be taken before the meal.

8.2 Distribution: SGLT2 inhibitors have high plasma protein binding (PPB). Dapagliflozin has 91% PPB; empagliflozin has 86% PPB and ertugliflozin has 93% PPB. Canagliflozin has the highest at 99% PPB. The Plasma protein binding is not significantly changed in patients with renal or hepatic impairment. The volume of distribution of canagliflozin, dapagliflozin(118L), ertugliflozin(85.5L), and empagliflozin(74L) suggests extensive tissue distribution.

8.3 Metabolism: SGLT2 inhibitors undergo biotransformation by UGT (uridine 5'-diphosphate-glucuronosyltransferases) mediated glucuronidation. Cytochrome P450 mediated metabolism of SGLT2 inhibitors is minimal. UGT1A9 plays an essential role in the metabolism of SGLT2 inhibitors. Canagliflozin is primarily metabolized by UGT1A9 and UGT2B4; ertugliflozin by UGT1A9 and UGT2B; dapagliflozin by UGT1A9 and empagliflozin is extensively metabolized by UGT2B7, UGT1A3, UGT1A8, and UGT1A9.

Excretion: SGLT2 inhibitors are filtered from plasma at the glomerulus and attach to the luminal membrane of the proximal convoluted tubule. The SGLT2 inhibitors attach to SGLT2 at the luminal membrane of the early segments of the nephron and prevent up to 60% of glucose reabsorption. SGLT2 inhibitors have a long elimination half-life allowing once-daily administration.

8.4 Mechanism of SGLT2: cotransporters (SGLTs) are proteins that occur primarily in the kidneys and play an important role in maintaining glucose balance in the blood. SGLT1 and SGLT2 are the two most known SGLTs of this family. SGLT2 is the major transport protein and promotes from the glucose back into circulation and is responsible for approximately 90% of the kidney's glucose reabsorption. SGLT2 is mainly expressed in the kidneys on the lining the first segment of the proximal convoluted tubule. By inhibiting SGLT2, gliflozins prevent the kidneys' reuptake of glucose from the glomerular filtrate and subsequently lower the glucose level in the blood and promote the excretion of glucose in the urine , how to give the action in our body SGLT-2 shown the basic mechanism which is summarized in **Figure 2.**

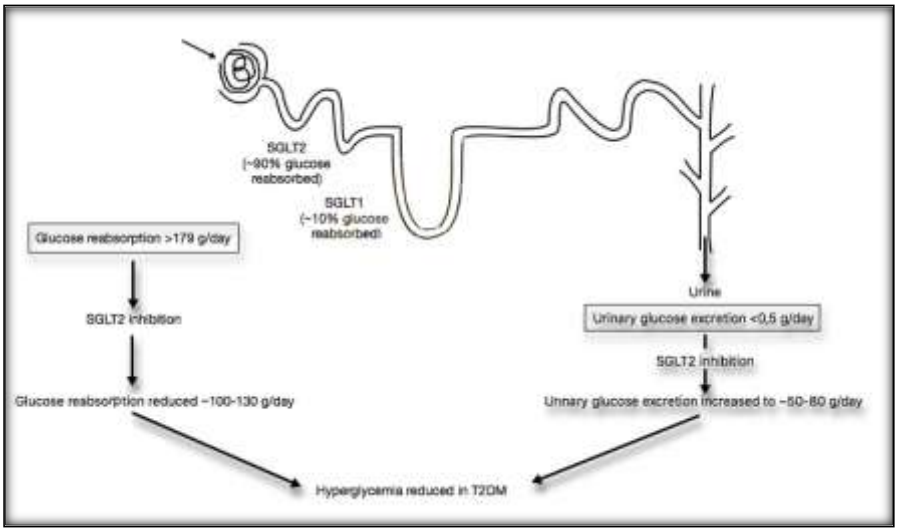

Figure 2. Mechanism of action of SGLT-2 inhibitors.

Transport protein and promotes from the glucose back into circulation and is responsible for approximately 90% of the kidney's glucose reabsorption. SGLT2 is mainly expressed in the kidneys on the lining the first segment of the proximal convoluted tubule. By inhibiting SGLT2,

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gliflozins prevent the kidneys' reuptake of glucose from the glomerular filtrate and subsequently lower the glucose level in the blood and promote the excretion of glucose in the urine. The mechanism of action on a cellular level is not well understood. However, it has been shown that binding of different sugars to the glucose site affects the orientation of the in the access vestibule. So when the aglycone binds it affects the entire inhibitor. Together these mechanisms lead to a synergistic interaction. Therefore, variations in the structure of both the sugar and the aglycone are crucial for the pharmacophore of SGLT inhibitors.

Dapagliflozin is an example of an SGLT-2 inhibitor, it is a competitive, highly selective inhibitor of SGLT. It acts via selective and potent inhibition of SGLT-2, and its activity is based on each patient's underlying. The results are decreased kidney reabsorption of glucose, glucosuria effect increases with higher level of glucose in the blood circulation. Therefore, dapagliflozin reduces the blood glucose concentration with a mechanism that is independent of insulin secretion and sensitivity, unlike many other. Functional pancreatic are not necessary for the activity of the medication so it is convenient for patients with diminished β- cell function.

Sodium and glucose are co-transported by the SGLT-2 protein into the tubular epithelial cells across the brush-border membrane of the. This happens because of the sodium gradient between the tubule and the cell and therefore provides a secondary active transport of glucose. Glucose is later reabsorbed by passive transfer of into the interstitial glucose transporter protein,

IX. (FIGURE 3.) PHARMA COKINETIC PARAMETERS OF VARIOUS SGLT-2 INHIBITORS

Name of drug	Bioavailability	Protein binding	tmax (hours)	t1/2 (hours)	Cmax	SGLT2 selectivity over SGLT1
Canagliflozin	65% (300 mg dose)	99%	1–2	10.6 (100 mg dose); 13.1 (300 mg dose)	1096 ng/mL (100 mg dose); 3480 ng/mL (300 mg dose)	250 fold
Dapagliflozin	78%	91%	1–1.5	12.9	79.6 ng/mL (5 mg dose); 165.0 ng/mL (10 mg dose)	1200 fold
Empagliflozin	90–97% (mice); 89% (dogs); 31% (rats)	86.20%	1.5	13.2 (10 mg dose); 13.3h (25 mg dose)	259nmol/L (10 mg dose); 687nmol/L (25 mg dose)	2500 fold
Ertugliflozin	70-90%	95%	0.5-1.5	11-17	268 ng/mL (15 mg dose)	2000 fold
Ipragliflozin (50 mg)	90%	96.30%	1	15–16 (50 mg dose)	975 ng/mL	360 fold
Luseogliflozin	35.3% (male rats); 58.2% (female rats); 92.7% (male dogs)	96.0–96.3%	0.625±0.354	9.24±0.928	119±27.0 ng/mL	1650 fold
Tofogliflozin (10 mg)	97.50%	83%	0.75	6.8	489 ng/mL	2900 fold

X. DIABETIC MANAGEMENT

10.1 Blood sugar monitoring:

Monitoringy our blood sugar(glucose)is key to determining how well your current treatment plan is working. It gives you information on how to manage your diabetes on a daily — and sometimes even hourly — basis. You can monitor your levels with frequent checks with a glucose meter and finger stick and/or with a continuous glucose monitor(CGM).You and your healthcare provider will determine the best blood sugar range for you.

10.2 Oral diabetes medications:

Oral diabetes medications (taken by mouth) help manage blood sugar levels in people

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who have diabetes but still produce some insulin — mainly people with Type 2 diabetes and prediabetes. People with gestational diabetes may also need oral medication. There are several different types. Metformin is the most common.

Insulin:

People with Type 1 diabetes need to inject synthetic insulin olive and manage diabetes. Some peoplewithType2 diabetes also require insulin. There are several different types of synthetic insulin. They each start to work at different speeds and last in your body for Blood pressure.

10.1.1 Cholesterol

Different lengths of time. The four main ways you can take insulin include injectable insulin with a syringe (shot), insulin pens, insulin pumps and rapid-acting inhaled insulin.

10.1.2 Diet

Meal planning and choosing a healthy diet for you are key aspects of diabetes management, as food greatly impacts blood sugar. If you take insulin, counting carbs in the food and drinks you consume is a large part of management. The amount of carbs you eat determines how much insulin you need at meals. Healthy eating habits can also help you manage your weight and reduce your heart disease risk.

10.1.3 Exercise:

Physical activity increases insulin sensitivity (and helps reduce insulin resistance), so regular exercise is an important part of management for all people with diabetes. Due to the increased risk for heart disease, it's also important to maintain a healthy

10.1.4 Weight.

XI. PREVENTION OF DIABETIES

You can't prevent autoimmune and genetic forms of diabetes. But there are some steps you can take to lower your risk for developing prediabetes, Type 2 diabetes and gestational diabetes, including:
Eata healthy diet,such as the Mediterranean diet.

- Get physically active. Aim for 30 minutes a day at least five days a week.
- Work to achieve a weight that's healthy for you.
- Manage your stress.
- Limit alcohol intake.
- Get adequate sleep (typically 7 to 9 hours) and seek treatment for sleep disorders.
- Quit smoking.

XII. FUTURE CHALLENGES

Given that the prevalence of diabetes is high at the population level, it imposes a financial burden on both our healthcare system and the individuals living with the disease. An attempt continues to be discussed; yet as the number of undiagnosed patients continues to grow, the prevalence and impact of the disease on patient quality of life and the overall cost of diabetes to healthcare is also important. The impact of diabetes is reaches in acrude state, it is essential to each country for implementation of preventive and curative measures. This may include restaurants to provide the caloric content of items on their menus; reduce the availability of high calorie, high-fat foods in school cafeterias; Lifestyle modification will undoubtedly play a key role in the ultimate solution to the problem of diabetes, and more definitive solutions will depend on the ability of basic science to point prevention and treatment in new direction Diabetes Mellitus is a heterogeneous metabolic disease, represented by diverse forms, each with a distinct pathophysiological origin but often manifest as a disorder with overlapping and difficult-to-differentiate characteristics. The treatment and management of each of these diabetic types are distinct in some characteristics but share a great deal of similarity as well as is the case with the disorder itself. All this emphasizes the importance of correct and timely diagnosis of each of these diabetic types and the critical role of their pathophysiological understanding. This is vital to safe guard diabetic individuals from exposures to potential adverse effects of improper, ineffective, or avoidable pharmaceutical interventions, which often delays the desired prognosis and increases the duration of hyperglycemic exposures. The long-term hyperglycemia, in turn, has often been associated with increased risk of microvascular and macrovascular diabetic complications, which affect the quality of life and mainly contribute to the diabetes-associated morbidity and mortality. For diabetes in general, and in particular, the diabetes types resulting from genetic mutations or associated genetic anomalies, the correct and timely molecular diagnosis can help in disease risk analysis and help in disease prediction and timely identification of individuals at an increased risk to the disorder, in particular, the family members. The predictive molecular/genetic testing and preventive

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management can play a vital role in such cases. Furthermore, irrespective of the diabetes type, various life style modifications and interventions such as extensive diet control, physical exercises, change of daily sedentary routine, and control of obesity are important in the prevention and the management of diabetes. The educational campaigns, which make the general population aware of the pathogenesis of this disease and the various controllable risk

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