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# A UPDATED REVIEW ON DIABETES MELLITUS

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**ABSTRACT**
Diabetes mellitus is a term used to describe a set of disorders that alter the body's blood sugar, or glucose. Diabetes is caused by either a lack of insulin production by the pancreas or a lack of insulin response by the body's cells. Diabetes is divided into two categories. Type 1 Diabetes and Type 2 Diabetes are the two types of diabetes. Insulin shortage and hyperglycemia are symptoms of type 1 diabetes, which is an autoimmune disease. Insulin is a hormone produced by the pancreas that aids in the transport of glucose into the body's cells for energy use. In India, diabetes prevalence increased from 7.1 percent in 2009 to 8.9 percent in 2019. IGT is anticipated to affect 25.2 million adults, with that number expected to rise to 35.7 million by 2045.Diabetes affected 1.3 billion Indians, or about four times the population of the United States. In 2017, 72.9 million people in India had diabetes, up from 40.9 million in 2007. Sodium-glucose co-transporter-2 (SGLT2) inhibitors (SGLT2i) are one of the most promising novel anti-diabetics, gaining attention even outside of its usual prescription for type 2 diabetes (T2DM). SGLT2 is a low-affinity, high-capacity glucose transporter that is expressed apically in proximal convoluted tubule epithelial cells and reabsorbs 90% of filtered glucose. SGLT2 inhibitors are a family of winkle GArgprescription drugs that have been licensed by the FDA for use in adults with type 2 diabetes in conjunction with diet and exercise to control blood sugar levels.

**KEYWORDS:** Diabetes mellitus, Empagliflozin, Glucose, hyperglycemia, hypoglycemia, Insulin.

## Diabetes

Diabetes mellitus refers to a group of diseases which affect the body blood by sugar i.e., glucose. Glucose plays a vital role for health because it is an important source of energy for the cells that make up the muscles and tissues. Glucose is the main source of fuel for brain.[1]

Diabetes mellitus is a group of metabolic diseases having high blood sugar levels for prolonged periods. This high blood sugar level produces the symptoms of frequent urination, increased thirst and hunger. This may lead to many complications if not treated timely. Acute complications include diabetic ketoacidosis and nonketotic hyperosmolar coma. Severe long-term complications include heart disease, stroke, kidney failure, foot ulcers and damage to the eyes. Diabetes is due to either the pancreas not producing enough insulin or the cells of the body not responding properly to the insulin produced.[2]

## Types of Diabetes

There are two types of Diabetes.

1. Type 1 Diabetes.
2. Type 2 Diabetes.[3]

## Type 1 Diabetes

Type 1 diabetes is an autoimmune disorder characterized by insulin deficiency and hyperglycemia. Earlier this was known as insulin dependent diabetes, a cellular mediated autoimmune process causes the destruction of beta cells of the pancreas. Only 5-10% of people are suffered by this type of diabetes.[4]

## Type 2 Diabetes

Insulin is a hormone synthesized by the pancreas which helps in making glucose into the cells of the body for energy usage. Insulin resistance occur when cells in the body does not responded properly to the insulin.[5]

## Prevalence of Diabetes

The prevalence of diabetes in India raised from 7.1% in 2009 to 8.9% in 2019. 25.2 million adults are estimated to have IGT, which is estimated to increase to 35.7 million in the year 2045.[6]

In India, 1.3 billion people roughly four times the population of the United States had diabetes. 72.9 million people in India had diabetes in 2017, which increased from 40.9 million in 2007. Type 2 diabetes is caused by insulin resistance and the pancreas slowly

losing the ability to make insulin.

Genes, environment and lifestyle are factors that can contribute to the development of type 2 diabetes.[7]

Type 1 diabetes is an autoimmune condition that results from attacking beta cells in the pancreas that makes insulin.[8] According to 2015 research, this is increasing by about 3 to 5 % per year and type 2 diabetes increased by an average of almost 8 % per year in urban areas.

**Reason behind the increase in diabetes prevalence in India**

-Lack of education
-Vegetarian food choices (high in carbohydrates, oils and fats)
-Increased consumption of processed meats
-Low consumption of fruits, nuts, seeds & whole grains
-Less exercise
-More screen times
-Tobacco use
-Alcohol use
-Environmental pollution
-High blood pressure
-High cholesterol levels
-Obesity
-Higher waist circumference
-Family history of diabetes

People of Asian descent may also have more visceral fat which increases the risk of diabetes.

The prevalence of diabetes is 11.8% in people aged above 50, according to a government survey. Highest prevalence of diabetes was observed in the 70-79 years age group at 13.2%.

Age and gender wise prevalence of diabetes in the population aged ≥ 50 years.[9]

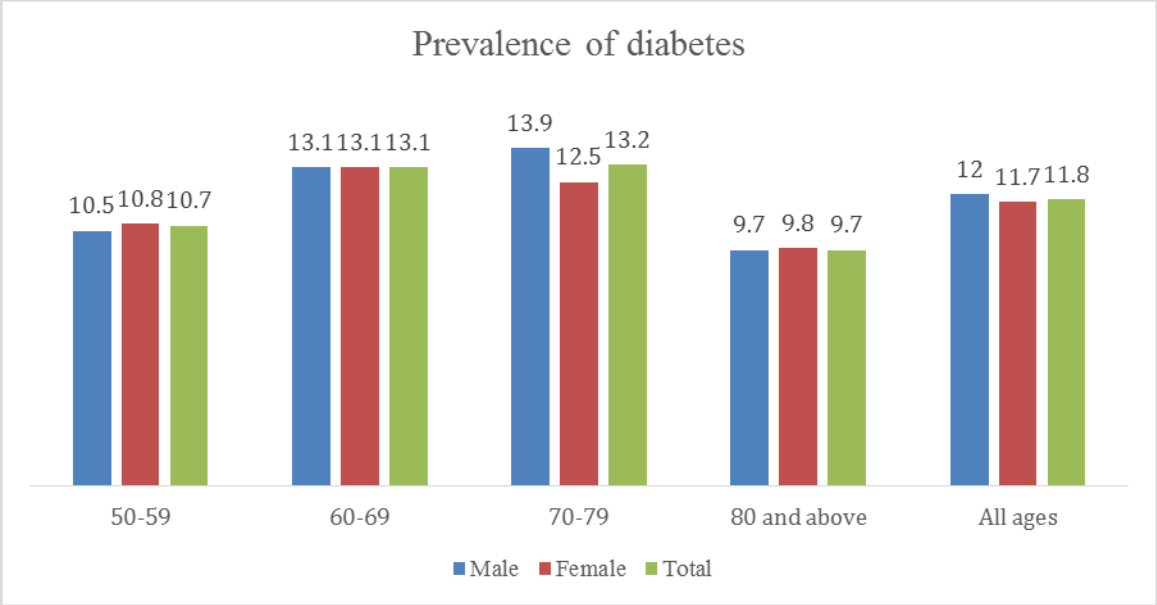



***Fig. 1:***

**Pathophysiology of Diabetes**

Insulin is the principal hormone that regulates the uptake of glucose from the blood into the cells of the body, especially liver, adipose tissue and muscle, except smooth muscle, in which insulin acts via the IGF-1 (insulin like growth factor-1). The deficiency of insulin or the insensitivity of its receptors plays a central role in all forms of diabetes mellitus. The body obtains glucose from intestinal absorption of food, breakdown of glycogen found in the liver and gluconeogenesis. Gluconeogenesis is the process of generation of glucose from non-carbohydrate substrates in the body. Insulin plays a critical role in all above-mentioned process.[10]

Insulin is released into the blood by a beta-cell found in the islet of Langerhans in the pancreases, in response to rising levels of blood glucose, typically after eating. Lower glucose levels result in decreased insulin release from the beta cells and results in the breakdown of glycogen to glucose. The process is mainly controlled by the hormone glucagon, which acts in opposite manner to insulin. The amount of insulin available is insufficient responding poorly to the effects of insulin and if the insulin itself is defective then, glucose will not absorb properly in the body cells.[11]

The net effect is persistently high levels of blood glucose, poor protein synthesis, and break down of fat storage. The glucose concentration in the blood remains high over time, the kidneys will reach a threshold of reabsorption i.e., glycosuria increases the osmotic pressure of the urine i.e., polyuria which leads to increased fluid loss. Lost blood volume will be replaced osmotically from water held in body cells and other body

compartments. The all leads to dehydration and then to polydipsia.[12]

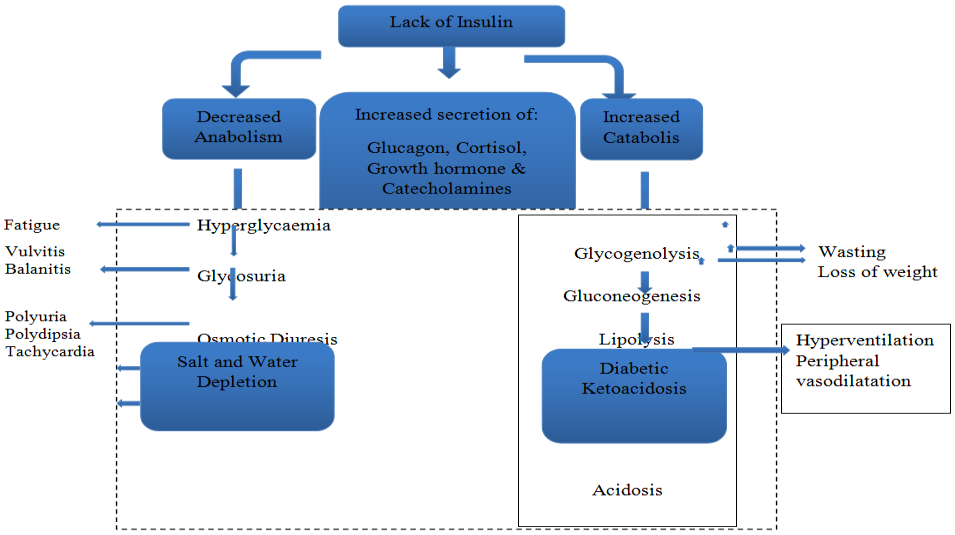



***Table 1.1:*** **Classification of Antidiabetic drugs.**

| DRUG CLASS | AGENT |
|---|---|
| **Sulfonylureas** | **First generation** |
| | Acetohexamide (Dymelor) |
| | Chlorpropamide (Diabinese) |
| | Tolazamide (Tolinase) |
| | Tolbutamide (Orinase) |
| | **Second generation** |
| | Glyburide (Micronase) |
| | Glipizide (Glucotrol) |
| | Glimepiride (Amaryl) |
| **Meglitinides** | Repaglinide (Prandin) |
| | Nateglinide (Starlix) |
| **Biguanides** | Metformin (Glucophage) |
| **Thiazolidinediones** | Pioglitazone (Actos) |
| | Rosiglitazone (Avandia) |
| **Alpha-glucosidase inhibitors** | Acarbose (Precose) |
| | Miglitol (Glyset) |
| | Voglibose |
| **SGLT2 Inhibitors** | Alpha Empagliflozin |
| | Dapagliflozin |
| | Canagliflozin |
| | Ertugliflozin |
| **Dipeptidyl Peptidase-4** | Sitagliptin |
| **(DPP-4) inhibitor** | Vildagliptin |
| | Saxagliptin |
| | Teneligliptin |
| | Alogliptin |
| | Linagliptin |
| **Dopamine D2 agonist** | Bromocriptine |
| **Others** | Pramlintide[13] |

**Treatment / Management**

**SGLT-2 Inhibitors**

Sodium-glucose co-transporter-2 (SGLT2) inhibitors (SGLT2i) are perhaps the most exciting newer anti-diabetics, which now have garnered attention even beyond its traditional indication for type-2 diabetes mellitus (T2DM). The clinical dimension of SGLT2i is increasing apart from frontline metabolic, cardiovascular, and renal therapeutics. A plethora of extra cardiac and renal effects are on the horizon and have not been told.

Some of these untold stories related to beyond glycemic lowering need serious considerations after they have been found to have some unique features and indications in some landmark trials.[16]

Empagliflozin is a medicine used to treat type 2 diabetes. Type 2 diabetes is a condition where the body does not make enough insulin, or the insulin that it makes does not work properly. This can cause high blood sugar levels (hyperglycaemia). It can also be taken together with other diabetes medicines, such as insulin, if a single diabetes medicine is not controlling the blood sugar level of diabetic patient properly.

Empagliflozin is only available on prescription. It comes as tablets usually taken once a day. Empagliflozin works by increasing the amount of sugar that leaves during urination. If empagliflozin is taken along with other diabetes medicines, it can sometimes cause low blood sugar (hypoglycaemia). Unlike some diabetes medicines, empagliflozin does not lead to weight gain. In fact, some people find they lose weight.

Empagliflozin also comes in association with other diabetes medicines like Synjardy i.e., Empagliflozin with metformin and Glyxambi i.e., empagliflozin with linagliptin.[17]

**SGLT2 Inhibitors History**

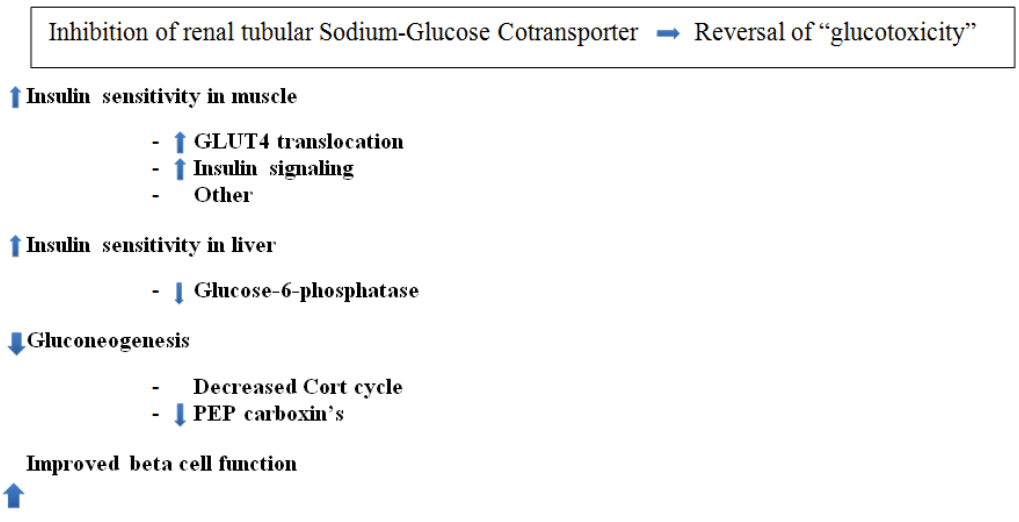
SGLT2 has a remarkable history dating back more than 150 years. It was first isolated from the root bark of apple trees as a substance called Phlorizin as early as 1835. The first clue about how kidneys reabsorb glucose came in the early 1980s. The first SGLT2i, which was approved by FDA was canagliflozin in 2013. Later dapagliflozin and empagliflozin were approved by FDA in January 2014 and August 2014, respectively. Ertugliflozin got approved by the FDA in 2017. Remogliflozin is approved by the health regulatory authority in India in 2019. Today SGLT2i is being successfully used to treat diabetes by harnessing the kidneys. This journey of SGLT2i is going through an unimaginable curve showing tremendous benefits to meeting the multitudes of unmet needs of diabetic patients.[18]

**SGLT2 Inhibitors Types**

- **Invokana (canagliflozin):** It helps the adults with type 2 diabetes by
  - Managing blood sugar
  - Reducing the risk of severe cardiovascular complications in adults with both type 2 diabetes and cardiovascular disease
  - Lowering the risk of kidney disease, cardiovascular death and hospitalization for heart failure in adults with both type 2 diabetes and diabetic nephropathy.
- **Farxiga (dapagliflozin):** Farxiga is recommended for both type 2 diabetes and heart failure. It also works as Invokana (canagliflozin).
  - manage the blood sugar
  - reduces the risk of hospitalization for heart failure in adults with both type 2 diabetes and cardiovascular disease
  - reduce the risk of cardiovascular death and hospitalization in adults with heart failure with reduced ejection fraction
  - lowers the risk of further worsening of kidney disease and slow the progression toward end-stage kidney disease
- **Jardiance (empagliflozin):** It helps the adults with type 2 diabetes by:
  - improving blood sugar
  - reducing the risk of cardiovascular death in adults with both type 2 diabetes and cardiovascular disease
- **Steglatro (ertugliflozin):** Stag Lotro can be used in adults with type 2 diabetes to improve management of blood sugar.

Patient with type 2 diabetes may be prescribed an SGLT2 inhibitor along with other diabetes medication life metformin.[19]

**Mechanism of Action SGLT2 inhibitors**



**Pathophysiology of SGLT2 Inhibitors**

SGLT2 is a low affinity, high-capacity glucose transporter which is expressed apically in epithelial cells of the proximal convoluted tubule and accomplishes reabsorption of ~90% of filtered glucose. Approximately 10% of glucose that escapes reabsorption by SGLT2 is subsequently resorbed by high-affinity low-capacity SGLT1, which expressed apically in epithelial cells of the straight descending proximal tubule.[20] To provide energy required to drive glucose transport against its concentration gradient, both SGLT2 & SGLT1 couple glucose transport across the apical cell membrane to the electrochemical gradient generated by active sodium-potassium transport by adenosine triphosphatase on the basolateral membrane.SGLT2 inhibitors block the reabsorption of glucose and sodium in the proximal tubule. The NaCl delivery enhances to JGA by reversing these pathophysiological changes, reducing intraglomerular pressure and preserving renal function.[21]

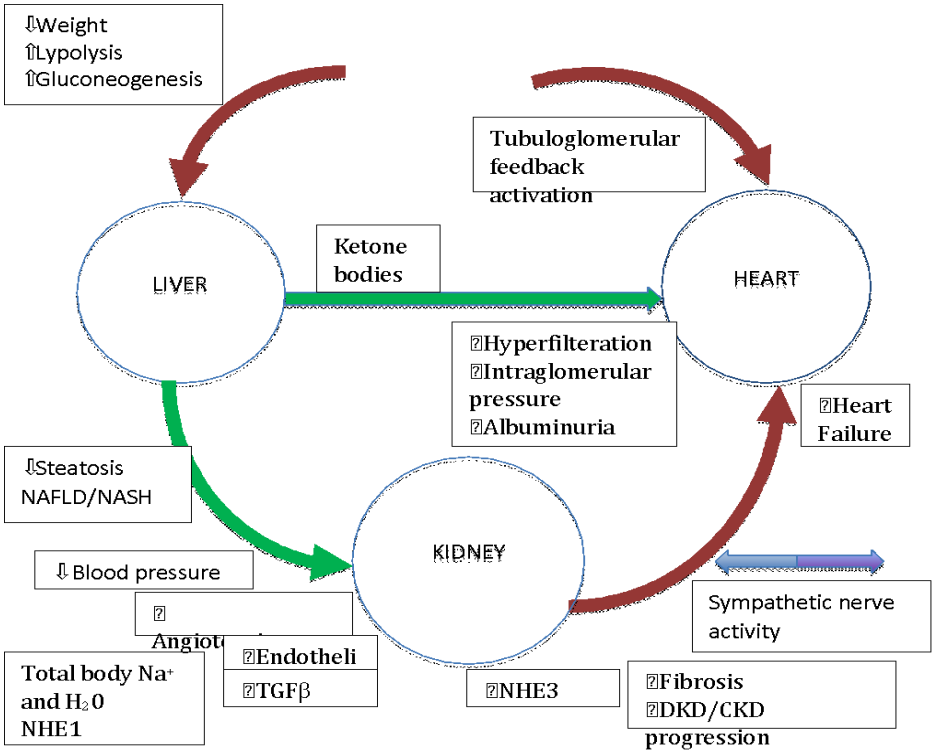



***Fig. 3.***

**SGLT2 as a drug target in diabetes**

- Kidney as a major site of glucose flux
- Unregulated in diabetes
- SGLT2 plays a role in renal glucose reabsorption in proximal tubule
- Renal glucose reabsorption is increased in type 2 diabetes
- Selective inhibition of SGLT2 increases urinary glucose excretion, reducing blood glucose
- Approach based upon benign autosomal genetic disorder resulting from mutations in genes encoding SGLT2 (familial renal glucosuria)
- Potential for weight loss
- Low risk for hypoglycemia.[22]

**SGLT2 Inhibitors and Heart failure**

According to a report in the Journal of the American Heart Association Trusted Source, having diabetes is a risk factor for heart failure. They noted the several recent studies on cardiovascular outcomes in type 2 diabetes who have been administered with SGLT2 inhibitors are less hospitalized due to heart failure. SGLT2 inhibitors reduced the risk of hospitalization for heart failure by 23 percent.

This benefit was seen in individuals regardless of their history of heart failure, other cardiovascular conditions, or hardened arteries.

SGLT2 inhibitors can also be beneficial for people without type 2 diabetes.

It is reported in a study in 2019 that Farxiga (dapagliflozin) lowered the risk of worsening heart failure or death due to heart failure with reduced ejection fraction (or, how much blood a heart ventricle pumps out with each contraction) in people with and without type 2 diabetes.

The FDA approved Farxiga (dapagliflozin) to treat this type of heart failure in 2020. It's possible that additional SGLT2 inhibitors may be approved for heart failure in the future, but additional clinical trials are necessary.

**Sglt2 Inhibitors for Diabetes**

The U.S. Food and Drug Administration (FDA) is warning that the type 2 diabetes medicines canagliflozin, dapagliflozin and empagliflozin may lead to ketoacidosis, a serious condition where the body produces high levels of blood acids called ketones that may require hospitalization, continuing to investigate this safety issue and will determine whether changes are needed in the prescribing information for this class of drugs, called SGLT2 inhibitors.

Patients should pay close attention for any signs of ketoacidosis and seek medical attention immediately if they experience symptoms such as difficulty breathing, nausea, vomiting, abdominal pain, confusion, and unusual fatigue or sleepiness. Do not stop or change diabetes medicines without any consultation with the prescriber. Health care professionals should evaluate for the presence of acidosis, including ketoacidosis, in patients experiencing these signs or symptoms. Discontinue SGLT2 inhibitors if acidosis is confirmed and take appropriate measures to correct the acidosis and monitor sugar levels.

SGLT2 inhibitors are a class of prescription medicines that are FDA approved for use with diet and exercise to lower blood sugar in adults with type 2 diabetes. When untreated, type 2 diabetes can lead to serious problems, including blindness, nerve and kidney damage, and heart disease. SGLT2 inhibitors lower blood sugar by causing the kidneys to remove sugar from the body through the urine. These medicines are available as single-ingredient products and also in combination with other diabetes medicines such as metformin. The safety and efficacy of SGLT2 inhibitors have not been established in patients with type 1 diabetes and FDA has approved them for use in these patients.

A search of the FDA Adverse Event Reporting System (FAERS) database identified 20 cases of acidosis reported as diabetic ketoacidosis (DKA), ketosis in patients treated with SGLT2 inhibitors from March 2013 to June 6, 2014. All patients required emergency room visits or hospitalization to treat the ketoacidosis. Since June 2014, continued to receive additional FAERS reports for DKA and ketoacidosis in patients treated with SGLT2 inhibitors.

DKA, a subset of ketoacidosis or ketosis in diabetic patients, is a type of acidosis that usually develops when insulin levels are too low or during prolonged fasting. DKA most commonly occurs in patients with type 1 diabetes and is usually accompanied by high blood sugar levels. The FAERS cases were not typical for DKA because most of the patients had type 2 diabetes and their blood sugar levels, when reported, were only slightly increased compared to typical cases of DKA. Factors identified in some reports as having potentially triggered the ketoacidosis included major illness, reduced food and fluid intake, and reduced insulin dose.

**Table 1.2: FDA Approval of Drug.**

| SGLT2 INHIBITOR | FDA APPROVAL | INDICATIONS | DOSE |
|---|---|---|---|
| **Invokana (canagliflozin)** | **2013** | Type 2 diabetes | 100 – 300 mg daily |
| **Farxiga (dapagliflozin)** | **2014** | Type 2 diabetes Heart failure | **Type 2 diabetes:** 5 – 10 mg daily **Heart failure:** 10 mg daily |
| **Jardiance (empagliflozin)** | **2014** | Type 2 diabetes | 10 – 25 mg daily |
| **Steglatro (ertugliflozin)** | **2017** | Type 2 diabetes | 5 – 15 mg daily[24] |

**SGLT2 Inhibitors: - Empagliflozin**

Empagliflozin is used in adult patients with type 2 diabetes either alone or in combination with metformin and linagliptin. It's also used to lower the risk of cardiovascular death in adults with type 2 diabetes mellitus and a history of cardiovascular disease.

In January 2020, the FDA certified an extended-release combination drug combining empagliflozin, metformin, and linagliptin for improving glycemic control in individuals with type 2 diabetes mellitus when used in conjunction with diet and exercise. In adult patients with heart failure, empagliflozin is also recommended to lower the risk of cardiovascular death and hospitalization owing to heart failure. In Europe, empagliflozin is used to treat symptomatic chronic heart failure with a decreased ejection fraction in adults.

Empagliflozin is not approved for use in patients with type 1 diabetes.

**Background of Empagliflozin:** Empagliflozin is a sodium-glucose co-transporter-2 inhibitor (SGLT2). The SGLT2 is predominantly responsible for glucose reabsorption in the kidney. It is used in the treatment of type 2 diabetes mellitus as a supplement to diet and exercise, and is frequently used in conjunction with other pharmacological interventions.

Phlorizin, the first known SGLT inhibitor, was discovered from apple tree bark in 1835 and studied extensively into the twentieth century, but it was eventually considered unsuitable for therapeutic intervention due to its lack of specificity and substantial gastrointestinal complications. The discovery of O-glucoside analogues of phlorizin (e.gremogliflozin etabonate) was the first attempt to overcome these constraints, however these compounds proved pharmacokinetically problematic.

Canagliflozin was approved by the FDA in 2013, and

dapagliflozin and empagliflozin were approved in 2014. Empagliflozin, the latest of the "flozin" drugs, has the highest SGLT2 selectivity over SGLT1 (approximately 2700-fold). The European Medicines Agency (EMA) approved empagliflozin in March 2022, making it the first and sole prescription for individuals with symptomatic chronic heart failure irrespective of ejection fraction.

**Chemical structure**

IUPAC name of empagliflozin is (2S,3R,4R,5S,6R)-2-[4-chloro-3-[[4-[(3S)-oxolan-3-yl] {oxy phenyl]methyl] phenyl]-6-(hydroxymethyl) oxane-3,4,5-triol.

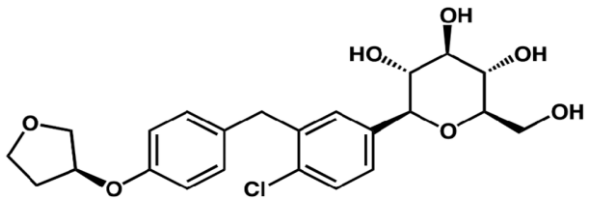



**Fig. 4:**

**Synthesis of Drug (Empagliflozin)**

Its molecular formula is C23H27ClO7 and the molecular weight is 450.91. Empagliflozin is a white to yellowish, non-hygroscopic powder. It is very slightly soluble in water, sparingly soluble in methanol, slightly soluble in ethanol and acetonitrile; soluble in 50% acetonitrile/water; and practically insoluble in toluene.

It developed and reported a concise, robust process for the production of empagliflozin on a metric ton scale. The synthesis is based on a highly b-selective AlCl3-promoted silane reduction of a methyl b-glycopyranoside. The one-stage process involves four chemical transformations starting from 5-halo-2-chlorobenzoic acids without isolation of intermediates and precise control over the purity profile of the final drug substance. It reported the synthesis of carbon-13 and carbon-14 labeled empagliflozin. The carbon-13 labeled empagliflozin in five steps and in 34% overall chemical yield starting from the commercially available a-D-glucose-[13C6]. For the radio synthesis, the carbon-14 atom was introduced in three different positions of empagliflozin. In the first synthesis, carbon-14 D-(þ)-gluconic acid d-lactone was used. It is prepared carbon-14 specifically labeled empagliflozin in carbon-1 of the sugar moiety. This four step-synthesis gave the desired material in 19% overall radiochemical yield and with a specific activity of 57.5 mCi/mmol and a radiochemical purity of 99.2%. Carbon-14 labeled empagliflozin with the radioactive atom in the benzylic position was obtained in eight steps and in 7% overall radiochemical yield with a specific activity of 54.3 mCi/mmol and a radiochemical purity of 98.9%. In the last synthesis carbon-14 uniformly labeled phenol was used to give [14C] empagliflozin in eight steps and in 18% overall radiochemical yield with a specific activity of 53.4 mCi/mmol and a radiochemical purity of 98.6%. Labeled empagliflozin was indispensable in DMPK and other studies.

**Mechanism of Drug**

The bulk of glucose filtered through the glomerulus is reabsorbed in the proximal tubule, largely by SGLT2 (sodium-glucose linked co-transporter-2), which accounts for 90% of total glucose reabsorption in the kidneys. The Na+/K+-ATPase enzyme on the basolateral membrane of proximal tubular cells uses ATP to actively pump Na+ ions into the interstitium surrounding the tubule, forming a Na+ gradient within the tubular cell. This gradient is then used by SGLT2 on the apical membrane of these cells to facilitate secondary active co-transport of both Na+ and glucose out of the filtrate, allowing glucose to be reabsorbed back into the bloodstream; inhibiting this co-transport allows for a significant increase in glucosuria and a decrease in blood glucose levels. Empagliflozin is a strong inhibitor of renal SGLT2 transporters found in the kidney's proximal tubules that lowers blood glucose levels by increasing glucosuria.

Independent of its blood glucose-lowering effects, empagliflozin appears to provide cardiovascular advantages, particularly in the prevention of heart failure, albeit the exact mechanism of this benefit is unknown.

Several theories have been proposed, including the inhibition of Na+/H+ exchanger (NHE) 1 in the myocardium and NHE3 in the proximal tubule, reduction of preload via diuretic/natriuretic effects and blood pressure reduction, prevention of cardiac fibrosis via suppression of pro-fibrotic markers, and reduction of pro-inflammatory adipokines.

The sodium-glucose co-transporter-2 (SGLT-2) located in the proximal tubules of the kidneys is inhibited by empagliflozin. Empagliflozin lowers glucose reabsorption in the kidneys and increases glucose excretion in the urine via inhibiting SGLT2. The drug has a glucose-lowering effect that is not dependent on insulin. In type 2 diabetes patients, urinary glucose excretion increased by approximately 64 g per day with 10 mg of empagliflozin and 78 g per day with 25 mg. Empagliflozin's diuretic and natriuretic characteristics cause intravascular contraction by lowering salt and volume load. Furthermore, empagliflozin is linked to weight loss and blood pressure decreases without an increase in heart rate.

Empagliflozin, also known as Jardiance, is a type 2 diabetes medicine that is used in combination with diet and exercise to treat the problem. It has advantages over sulfonylureas and can be used instead of metformin. [8] It can be used with other drugs like metformin or insulin. It is not advised for people with type 1 diabetes. It is taken orally. In view of recent trial evidence, it is expected to soon receive authorization to be used for patients with heart failure, irrespective of diabetic status. Jardiance can also be used to lower cardiovascular

mortality in patients with coronary heart failure.

Urinary tract infections, groin fungal infections and joint problems are also common adverse effects. Fournier's gangrene, a skin infection of the groin, and diabetic ketoacidosis with normal blood sugar levels are two rare but significant adverse effects. It is not advised to use during pregnancy or while breastfeeding. It is not suggested for people who have severe renal disease, although it may tend to delay the course of moderate kidney disorders. Empagliflozin is a sodium glucose co transporter-2 (SGLT-2) inhibitor that works by increasing sugar excretion in the urine.

In 2014, the United States and the European Union approved empagliflozin for medicinal usage. With over 4 million prescriptions written in 2019, it was the 146th most widely prescribed drug in the United States.

**Pharmacodynamics**

Empagliflozin lowers blood sugar by preventing glucose reabsorption in the kidney, thereby increasing the amount of glucose excreted in the urine. It has a relatively long duration of action and requires only one dose per day. Patients should be closely monitored for any signs or symptoms of ketoacidosis, regardless of blood glucose levels, because empagliflozin may precipitate diabetic ketoacidosis in the absence of hyperglycemia. Because its mechanism of action is dependent on renal glucose excretion, empagliflozin can be discontinued in patients with acute renal failure and discontinued in patients who develop chronic kidney disease.

Excessive secretion of glucose creates a sugar-rich urogenital environment that increases the risk of urogenital infections in both male and female patients.

**Uses of Drug**

Empagliflozin is used to control high blood sugar in people with type 2 diabetes. It may be used with other medicines for type 2 diabetes such as metformin, sulfonylureas, and insulin.

**Empagliflozin in Weight and blood pressure**

Controlling high blood sugar helps in preventing kidney damage, blindness, nerve problems, loss of extremities and problems with sexual function. Empagliflozin caused moderate effects on blood pressure and body weight.

These effects are probably due to urinary glucose excretion and slightly increased urinary sodium excretion. In clinical trials, patients receiving empagliflozin lost an average of 2% of baseline body weight. A higher percentage of people taking empagliflozin lost more than 5% of their baseline weight. The drug lowers systolic blood pressure by 3 to 5 mm of mercury (mmHg). The effects on blood pressure and body weight are generally considered favorable, as many type 2 diabetics have high blood pressure or are overweight or obese.

Empagliflozin is also used in people with type 2 diabetes and heart disease to reduce the risk of demise from a heart attack or stroke.

**Heart & kidney disease**

Empagliflozin appears to reduce the likelihood of hospitalization for patients with type 2 diabetes due to the progression of heart failure or chronic kidney disease. Empagliflozin may reduce the likelihood of death from cardiovascular causes in people with type 2 diabetes and known cardiovascular disease. One concern with the research on which these claims are based is that different weapons received different amounts of other drugs. Therefore, the reduced risk is not always due to empagliflozin. It is also approved in some countries to reduce the risk of death from cardiovascular causes in people with type 2 diabetes and heart disease.

Negative effects of Empagliflozin have a number of side effects including hypotension, ketoacidosis, acute kidney injury, genital yeast infections, hypoglycemia with insulin, dyslipidemia, Fournier gangrene and pyelonephritis. Empagliflozin causes osmotic diuresis and intravascular volume contraction and may therefore cause symptomatic hypotension, particularly in patients receiving diuretics, ACE inhibitors, or antagonists' angiotensin receptors. In the elder patients, renal impairment, myasthenia gravis and low arterial pressure are some notable adverse effects. Empagliflozin increases serum creatinine and decreases eGFR. Therefore, renal function should be assessed initially and monitored periodically. The use of empagliflozin is not recommended if the GFR is less than 45 mL/min and when the GFR is less than 30 mL/min/1.73 m^2, the drug is contraindicated. Empagliflozin has been associated with ketoacidosis, particularly in patients with type 1 diabetes, and therefore should not be used in this patient population. Predisposing factors for ketoacidosis are pancreatic disorders, history of pancreatitis, pancreatic surgery, alcohol abuse. The risk of hypoglycemia is increased when empagliflozin is used in combination with a sulfonylurea or insulin. Use caution when prescribing and consider reducing the dose of sulfonylurea. Empagliflozin increases the risk of genital yeast infections and urinary tract infections. Evaluate signs and symptoms and treat appropriately. Fungal diseases of the male genitals include balanitis, balanitis, scrotal abscess, and penile infections. Yeast infections in women include vulvo vaginitis and vaginal candidiasis. In women, urinary tract infections and genital yeast infections are more common than in men. A rare but serious bacterial infection is necrotizing fasciitis of the perineum; Fournier's gangrene. Symptoms begin as early as the first week of treatment and as late as two years after starting treatment.

Patients taking SGLT2 inhibitors should receive counseling about the risk of necrotizing fasciitis of the

perineum. Confirmed infections should be reported to the FDA by clinicians.

Empagliflozin works by increasing the excretion of sugar by the kidneys. Empagliflozin is also used to treat heart failure.

In August 2021, Jardiance (empagliflozin) was FDA-approved to treat ***HEART FAILURE WITH REDUCED EJECTION FRACTION*** (HFrEF) in people with or without diabetes. Jardiance is taken orally once in a day.

Ridgefield, Conn. and Indianapolis, August 18, 2021 – Jardiance (empagliflozin) 10 mg has been approved by the U.S. Food and Drug Administration to reduce the risk of cardiovascular death plus hospitalization for heart failure in adults with ***HEART FAILURE WITH REDUCED EJECTION FRACTION*** (HFrEF), Boehringer Ingelheim and Eli Lilly. It may help to live long and healthier life as it lowers the risk of going to the hospital for heart failure.[23]

## CONCLUSION

Diabetes is caused by a lack of insulin production by the pancreas or a lack of insulin responsiveness by the cells in the body. There are two types of diabetes: type 1 and type 2. The two kinds of diabetes are Type 1 Diabetes and Type 2 Diabetes. Type 1 diabetes, which is an autoimmune illness, causes insulin deficiency and hyperglycemia. Insulin is a hormone generated by the pancreas that helps glucose enter the body's cells for energy usage. Diabetes prevalence in India has increased from 7.1% in 2009 to 8.9% in 2019. IGT is estimated to affect 25.2 million adults by 2045, with that figure rising to 35.7 million. Diabetes afflicted 1.3 billion Indians, according to the World Health Organization.

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