EVALUATION OF COMPARATIVE EFFICACY AND PLEIOTROPHY OF THE AVAILABLE THREE SGLT2 INHIBITORS IN TYPE 2 DM SUBJECTS

Dissertation submitted in partial fulfillment of the Requirement for the award of the degree of

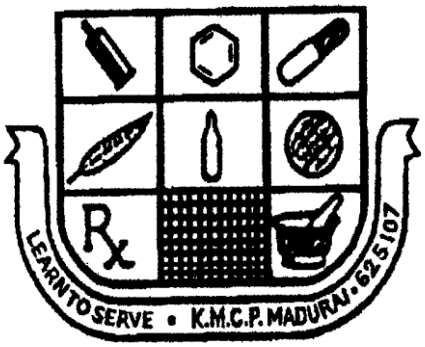
MASTER OF PHARMACY IN

PHARMACY PRACTICE

OF

THE TAMILNADU Dr M.G.R MEDICAL UNIVERSITY,

CHENNAI



DEPARTMENT OF PHARMACY PRACTICE

K.M.COLLEGE OF PHARMACY

UTHANGUDI,

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OCTOBER - 2016

CERTIFICATE

This is to certify that the dissertation entitled "**EVALUATION OF COMPARATIVE EFFICACY AND PLEIOTROPHY OF THE AVAILABLE THREE SGLT2 INHIBITORS IN TYPE 2 DM SUBJECTS"** submitted by **Mr.R.NATARAJAN** (**Reg. No.261440058)** in partial fulfillment for the award of **Master of Pharmacy** in **Pharmacy Practice** under **The Tamilnadu Dr.M.G.R Medical University**, Chennai, done at **K.M College of Pharmacy**, Madurai-625107.

It is a bonafide work carried out by him under my guidance and supervision during the academic year **OCTOBER-2016.** The dissertation partially or fully has not been submitted for any other degree or diploma of this university or other universities.

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ACKNOWLEDGEMENT

"Our Unknown future is secure in the hands of Our all knowing God"

I humbly submit this work to the Lord Almighty, without whom it would have been unsuccessful.

"Optimism is the faith that leads to achievement. Nothing can be done without Hope, Confidence and Perseverance"

This dissertation is certainly the result of that work, whereby I have been accompanied and supported by many People.

It affords me an immense pleasure to acknowledge with gratitude the help, guidance and encouragement rendered to me by all those eminent personalities to whom I owe a substantial measure for the successful completion of this endeavour.

First and foremost, I wish to express my deepest love and thanks to my beloved Parents, who left me to myself, To work to suffer, To learn and To build, To discover my own riches and To paddle my own canoes. Though Millions of Words are too short to express my love for You, thankyou for your unconditional love and sacrifices for me.

I prevail my deep sense of gratitude to **Prof.M.NAGARAJAN, M.Pharm., M.B.A., D.M.S.,(BM)., D.M.S(IM).,** Correspondent, K.M. College of Pharmacy, for his valuable guidance, inspiration, encouragement, and constant suggestions which endless helped me to completion of this project work successfully.

"It's in your moments of decision that your destiny is shaped"

Words are not enough to thank **Mrs.K.JEYASUNDARI, M.Pharm.,**Assistant Professor, Department of Pharmacy Practice, K.M. College of Pharmacy, for her most valuable guidance, motivation and helps in taking the correct decision at a correct time throughout this work.

I would like to express my profound sense of gratitude to **PROF.K.THIRUPATHI, M.Pharm.,** Professor & Head of the Department(Pharmacy Practice) for his valuable way of guidance, inspiration, encouragement, and constant suggestions which endless by helped me to complete this project work successfully.

It is my pleasant duty to express my deep sense of gratitude and indebtedness to **Dr.M.SUNDARAPANDIAN, M.Pharm., Ph.D.,** Principal and Head of the Department of Pharmaceutical Chemistry, K.M. College of Pharmacy for his valuable suggestions and constant inspiration.

I would like to express my profound sense of gratitude to **Dr.N.CHIDAMBARANATHAN,M.Pharm., Ph.D.,** Vice Principal and Head of the Department of Pharmacology, K.M. College of Pharmacy for his boundless help, valuable suggestions and encouragement in carrying out my project. Once again a Special thanks to him for his support, throughout my college life.

At the outset, I express my deep heartfelt and sincere thanks to **Dr.K.KANNAN.,M.D.,D.M.,FICP,BGL.,**Diabetologist and endocrinologist and **Dr.K.ARUN KANNAN M.D** for allowing me to accomplish the project work in their D.Diab-Endo clinic. They were always enthusiastic in suggestion, despite their extremely busy schedule. Their work always inspired me to think beyond what I could and encourage me to depute maximum efforts into my work.

My Heartfelt thanks to **Mrs.Daisy chithra, Miss. Kalayarasi,** and **Mrs.Mayadevi**, **Mrs.Subha, Mrs.Jeya, Mr.Pandi, Mr.Meenatchi Sundaram, Staff at MIDE** for their valuable contribution in completing this dissertation work.

It is my duty to say a special word of thanks to **Mrs.M.Shanthi B.A.,** Librarian and **Mrs.Latha kalyanasundari,Mrs.Sujitha,Mrs.Sharmila, Mr.Kumaraguru,Mrs.Uma,**and **my parents** & **K.M. College of Pharmacy** for their timely helps during this work.

"Friendship is the Happiness of Today and Promise of Tomorrow"Words are inadequate to express my deep sense of gratitude to my lovable colleagues especially Mr.Abbas**,Mr.Lenin,Mr.Karuppu,Mr.BalamuruganMr.Ramanathan,Mr.Vicram, Miss.Priya,Mrs.Anitha** for their friendship and support.

Also I would like to thank all my M.Pharm and B Pharm friends who helped me through their ideas and support.

I might have forgotten to name a few people, behind this work, but still really thank to all concerned individuals for their support to complete this work successfully in time.

CONTENTS

ABBREVIATIONS

eGFR-estimated Glomerular Filtration Rate

CKD-Chronic Kidney Disease

DM-Diabetes Mellitus

EGP-Endogenous Glucose Production

FPG-Fasting Plasma Glucose

GFR- Glomerular filtration rate

GGM-Glucose-Galactose Malabsorption

GLP-1- glucagon-like peptide-1

GLUT- glucose transporter

HDL-C- high-density lipoprotein cholesterol

HbA1C-Glycosylated hemoglobin.

LADA-Late onset autoimmune diabetes.

LDL-C-low-density lipoprotein cholesterol.

MODY-Maturity onset diabetes of the young.

PPBS-Post Prandial Blood Sugar.

RT_G-Renal threshold for glucose excretion.

RAAS-Renin Angiotensin Aldosterone system

SGLT- Sodium Glucose Co-Transporter

T_mG-Tubular Maximum Glucose reabsorptive capacity

T2DM-Type 2 diabetes mellitus

UGE-Urinary Glucose Excretion

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INTRODUCTION:

Type 2 diabetes mellitus (T2DM) is a chronic disease that is associated with obesity and the progressive development of hyperglycemia. Increased body fat is associated with the development of insulin resistance in muscle and in the liver, particularly if excess fat is deposited in these tissues . Initially, the pancreas is able to overcome this insulin resistance by producing more insulin, but in diabetes there is a progressive failure of β-cell output, resulting first in glucose intolerance and then overt T2DM. In addition to these established factors, it is now known that multiple defects, involving numerous metabolic pathways and organ systems, contribute to the progression of hyperglycemia in T2DM. It include adipocytes (accelerated lipolysis), the gastrointestinal tract (incretin deficiency/resistance), pancreatic α-cells (hyperglucagonemia), the brain (insulin resistance), and the kidneys (increased glucose reabsorption).[1]

Diabetes is a worldwide growing public health problem with high risks of severe micro vascular and macrovascular complications. Diabetic nephropathy (DN) is a major burden among the chronic complications of diabetes, given that it affects the 30% of patients with diabetes. Indeed, DN is the most common cause of end-stage renal disease . Known risk factors for DN include hyperglycemia, hypertension, dyslipidemia, smoking, and obesity as well as ethnic, familial, and genetic predispositions. Thus, large intervention trials on the impact of long-term intensified glucose control on chronic diabetes complications, both in type 1 and type 2 diabetes, have documented the critical role of glycemic control in preventing the development of early DN as well as in slowing its progression; In contrast, the clinical trials with renin-angiotensin-aldosterone system (RAAS) blockade versus other antihypertensive agents in primary prevention of DN have

provided conflicting results , when albuminuria is the primary outcome, by the rapid but reversible decreases in urinary albumin excretion rate and by the differences in blood pressure control.

Among the most recent glucose-lowering oral agents, the sodium–glucose cotransporter (SGLT) 2 inhibitors have the potential to exert nephro protection through improving glycemic control but also through glucose-independent effects, such as blood pressure–lowering and, possibly, some direct renal effects. Interestingly, SGLT2 inhibitors also have renal hemodynamic effects, including reducing glomerular hyperfiltration, as well as inhibitory effects on the inflammatory and fibrotic responses of proximal tubular cells to hyperglycemia. The SGLT2 is localized to the proximal tubule and is responsible for 90% of the reabsorption of the glucose filtered by the kidney. In type 2 diabetes, as a consequence of the increased glucose filtered load, there is an increased expression of SGLT2 and an increased reabsorption of glucose; this a maladaptive mechanism contributing to hyperglycemia . SGLT2 inhibition leads to substantial glycosuria and reduction in fasting and postprandial plasma glucose levels, without stimulating insulin secretion, and therefore without increasing the risk of hypoglycemia.[2]

Diabetes was firmly established as an endocrine disease, and the potential role of the kidney in the pathogenesis of diabetes was largely ignored. Interestingly, attention is once again focused on the kidney, not only as an organ that may be adversely affected by diabetes, but also as an important player in glucose homeostasis and a potential target for the treatment of hyperglycemia in type 2 diabetes.

SUBJECTIVE INTRODUCTION:

The kidney has historically been ignored as a potential target organ for the pharmacologic mitigation of hyperglycemia, as it was primarily considered an organ of elimination and a regulator of salt and ion balance. The kidney was once mistakenly thought to be the structural cause of diabetes, and in later years has essentially been ignored as a regulator of glucose homeostasis. Today, however, it is now recognized as an important contributor to glucose regulation. In line with this, we now have a clearer understanding of the physiology of glucose transport via specific carriers such as the sodium-glucose co-transporters (sodium-glucose linked transporters), or SGLTs.[3]

The kidneys are crucial for maintaining glucose homeostasis, and contribute to this process via glucose uptake, gluconeogenesis, and reabsorption of glucose from the glomerular filtrate into the circulation. On average, an individual's entire blood volume is filtered by the kidney more than 50 times daily, with around 160–180 g of glucose filtered from plasma by glomeruli every day (180 L per day at approximately 100 mg/dL of glucose). Under normal circumstances, this filtered glucose is almost completely reabsorbed in the proximal tubules of the kidney, leaving the urine free of glucose. The reabsorption of filtered glucose is mediated by SGLTs, a family of active, sodium-dependent, large trans-membrane proteins. Two members of the SGLT family are involved in glucose reabsorption in the kidney: SGLT2 is a high-capacity, low affinity transporter, expressed in the early convoluted segment of the proximal tubule, and has traditionally been thought to be responsible for nearly 90% of the active renal glucose re-absorption; while SGLT1, a high-affinity, low-capacity transporter, expressed in the distal segment of the proximal tubule,

reabsorbs the remaining 10%.SGLT2 is thought to be expressed exclusively in renal proximal tubules, but SGLT1 is also found in the gastrointestinal tract, where it is responsible for absorption of galactose as well as glucose.For both SGLTs, glucose reabsorbed from the proximal tubules by SGLTs is then passively diffused into the circulation via facilitative glucose transporters (GLUTs) at the basolateral membrane of the cells lining the proximal tubule. Glucose reabsorption in people with type 2 diabetes.

In patients with type 2 diabetes, blood glucose levels eventually become so high that they exceed the capacity of the SGLT2 transporters, at a threshold of approximately 200 mg/dL (11.0mmol/L). Thus, not all glucose is reabsorbed, and glucose begins to appear in the urine. Unfortunately, in patients with ongoing hyperglycemia, up-regulation of glucose transporter genes increases the level of renal glucose reabsorption. This increased threshold for glucose transport minimizes UGE and intensifies hyperglycemia; however, once this increased threshold is exceeded, the characteristic glucosuria is detected.[4]

In recent years, realistic options for promoting UGE via SGLT inhibition have been identified. Efforts have focused on selective SGLT2 inhibition, as this transporter is expressed almost exclusively in renal proximal tubules and its inhibition is therefore unlikely to affect other organ systems. Individuals who lack functional SGLT1 have severe gastrointestinal symptoms due to malabsorption of glucose and galactose, while people who lack a functional gene for SGLT2 generally lead normal healthy lives, despite the presence of higher-than-normal levels of glucose in their urine. In people lacking SGLT2 (a condition known as familial renal glycosuria), essential levels of glucose are maintained, and although SGLT2 normally transports around 90% of the 180 g of glucose reabsorbed, inhibition of SGLT2.

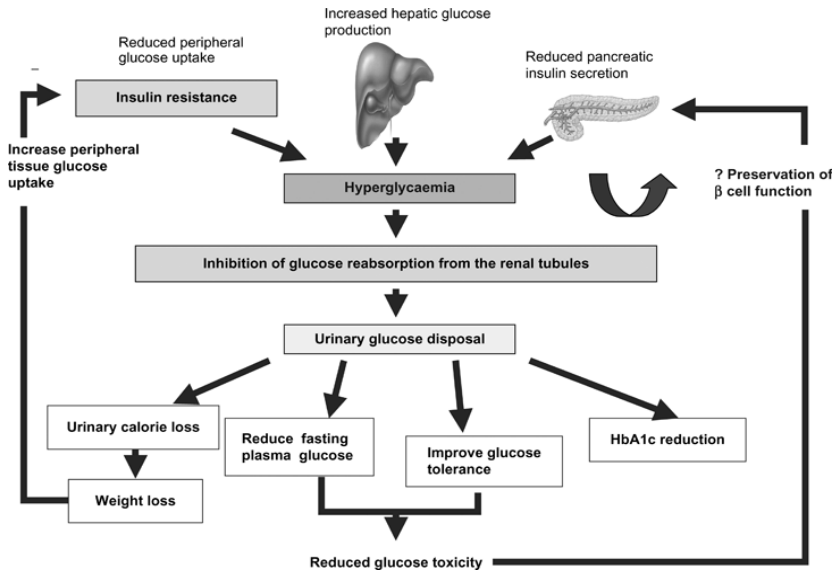

FIGURE 1: SODIUM GLUCOSE CO TRANSPORTER 2 INHIBITORS: AN EMERGING NEW CLASS OF ORAL ANTIDIABETIC DRUG

Typically only results in maximum excretion of about 50% (90 g) of glucose, suggesting that when SGLT2 is inhibited, SGLT1 capacity can be increased. Besides reduction in blood glucose, SGLT2 inhibition has the additional potential advantages of weight loss (corresponding to the calories lost daily in excreted glucose) as well as no increase in hypoglycemia (since insulin secretion is not stimulated) when used as monotherapy. Phlorizin, a compound originally isolated from the bark of apple trees, was the first SGLT inhibitor identified.

Despite its ability to induce glucosuria, phlorizin was not clinically developed because it had low bioavailability, degraded rapidly after oral administration to phloretin (a potent inhibitor of GLUT transporters), and inhibited SGLT1 In the early proximal tubule,90% of glucose filltered is reabsorbed by SGLT2,unless SGLT2 is inhibited.[5]

In the late proximal tubule,10% of glucose filltered is reabsorbed by SGLT1 Inhibition of SGLT2 significantly reduces filtered glucose being reabsorbed, and excess glucose is secreted into the urine In the small intestine, glucose is transported to the blood stream by SGLT1 cause Glucose Reduction in blood glucose level.

GLUCOSE HOMEOSTASIS AND THE KIDNEY:

Glucose regulation can be divided into three main processes: 1) glucose absorption, 2) glucose synthesis or production, and 3) glucose utilization.

Endogenous glucose production occurs primarily in the liver, with hepatic glycogenolysis and gluconeogenesis accounting for 85% of endogenous production. However, it is important to note that gluconeogenesis is responsible for about 55% of glucose released during the non-fed period and thus has a significant impact on glycemia. The kidney warrants consideration in the overall picture of endogenous glucose synthesis because renal glucose production accounts for about 20% of all overall endogenous glucose release and is also responsible for approximately 40% of glucose released secondary to gluconeogenesis. Therefore, the kidney plays an important role in glucose production.

After glucose is ingested, an increase in plasma glucose concentration triggers insulin release, which in turn stimulates splanchnic and peripheral glucose

uptake and suppression of endogenous glucose production. Under normal circumstances in healthy individuals, blood glucose levels are tightly regulated within the range of 70 to 99 mg/dL and rarely exceed 140 mg/dL following postprandial consumption. These narrow ranges are maintained under a complex system that includes multiple hormones (e.g., insulin and glucagon), central and peripheral nervous system metabolic needs, and various cells and tissues (e.g., brain, muscle, GI tract, liver, kidney, and adipose tissue), which regulate the uptake, metabolism, storage, and excretion of glucose.[6]

Two groups of glucose transporters mediate most cellular glucose transport: glucose transporters (GLUTs), which are expressed throughout the body, and SGLTs. The function of SGLTs will be discussed further below.

Glucose utilization takes place primarily (over 80%) in the muscle. This glucose is utilized directly for energy or stored as glycogen. Under normal conditions, approximately 5% of peripheral glucose is taken up by fat tissue. The liver preferentially stores absorbed glucose in the form of glycogen when under the influence of insulin.

With normal kidney function, 99% of filtered glucose is reabsorbed during periods of euglycemia. The glomerular filtration rate (GFR) and plasma glucose concentration govern the rate of glucose filtration. Under normal conditions, most if not all of the filtered glucose is reabsorbed. However, there is a maximum rate at which glucose can be reabsorbed (~375 mg/min in an average patient). The most salient SGLT in the kidney is SGLT2. SGLT2 accounts for approximately 90% of glucose reabsorption in the kidney and, because of this, has become the focus of this new category of medications, the SGLT2 inhibitors. SGLT2 transporters are found at a relatively high density on the brush-border

membrane of the S1 (early) segment of the proximal convoluted tubule. This transporter binds with both sodium ions (Na^+) and glucose in the tubular filtrate. These compounds are then translocated across the cell membrane. Functionally, this process is driven by the electrochemical Na^+ gradient between the tubular filtrate and the intracellular space and is called *secondary active-transport*. Glucose in the tubular epithelial cell is then transported down a concentration gradient across the basolateral membrane to the systemic circulation by GLUT1.[7]

When the rate of glucose absorption exceeds 375 mg/min, glucose is excreted in the urine because its concentration has exceeded the ability of the SGLT2 transporters to reabsorb it. In most non diabetic persons, glucose concentrations will never be high enough to exceed the kidney's ability to reabsorb the presented glucose. However, in patients with diabetes, glucosuria is common with blood glucose of 180 mg/dL or higher.SGLT2 inhibitors modulate this pathway by reducing the reabsorptive capacity of the renal tubules, with a resultant elimination of excess glucose.

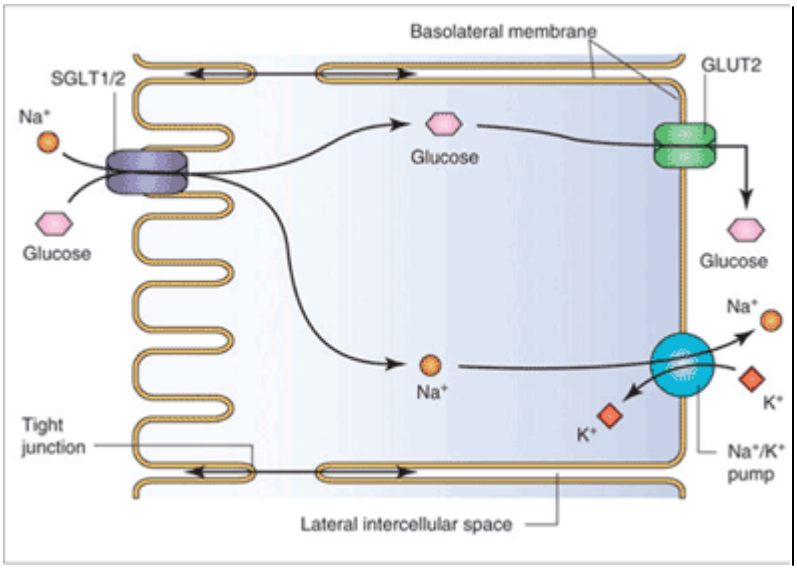

FIGURE 2: GLUCOSE REABSORPTION FROM THE GLOMERULAR FILTERATE THROUGH A PROXIMAL TUBULE EPITHELIAL CELL INTO BLOOD.

Thus, the mechanism of action of the SGLT2 inhibitors is to simply inhibit the transporter, which in turn reduces the reabsorption of filtered glucose and lowers the renal threshold for glucose. The two main sodium–glucose co transporters (SGLTs), SGLT1 and SGLT2, provide new therapeutic targets to reduce hyperglycaemia in patients with diabetes. SGLT1 enables the small intestine to absorb glucose and contributes to the reabsorption of glucose filtered by the kidney.

SGLT2 is responsible for reabsorption of most of the glucose filtered by the kidney. Inhibitors with varying specificities for these transporters (eg, dapagliflozin, canagliflozin, and empagliflozin) can slow the rate of intestinal glucose absorption and increase the renal elimination of glucose into the urine. Results of randomised clinical trials have shown the blood glucose-lowering efficacy of SGLT inhibitors in type 2 diabetes when administered as mono therapy

or in addition to other glucose-lowering therapies including insulin. Increased renal glucose elimination also assists weight loss and could help to reduce blood pressure. Effective SGLT2 inhibition needs adequate glomerular filtration and might increase risk of urinary tract and genital infection, and excessive inhibition of SGLT1 can cause gastro-intestinal symptoms. However, the insulin-independent mechanism of action of SGLT inhibitors seems to offer durable glucose-lowering efficacy with low risk of clinically significant hypoglycaemia at any stage in the natural history of type 2 diabetes. SGLT inhibition might also be considered in conjunction with insulin therapy in type 1 diabetes.

The kidney plays a central role in the regulation of plasma glucose levels.The sodium glucose co-transporter type 2 (SGLT2) located in the plasma membrane of cells lining the proximal tubule mediates the majority of renal glucose reabsorption from the tubular fluid, which normally prevents the loss of glucose in the urine. Competitive inhibitors of SGLT2 that provoke the renal excretion of glucose have been discovered, thereby providing a unique mechanism to potentially lower the elevated blood glucose levels in patients with diabetes.[8]

The kidney contributes to the maintenance of blood glucose levels primarily by the reabsorption of glucose from the glomerular filtrate to the blood. Under normal conditions, almost all of the filtered glucose is reabsorbed and returned to the circulation in the proximal tubule of the nephron. Glucose is reabsorbed by sodium-glucose co transporters (SGLTs) in concert with facilitative glucose transporters (GLUTs).

The ability of the kidneys to reabsorb glucose is limited by the capacity of these transporters, and as plasma concentrations exceed ~ 180–200 mg/dl (the renal threshold), glucose starts to appear in the urine. Kidneys continue

to reabsorb glucose even in the presence of abnormally high plasma glucose concentrations

The kidney plays a major role in glucose homeostasis because of its role in gluconeogenesis and the glomerular filtration and reabsorption of glucose in the proximal convoluted tubules. Approximately 180 g of glucose is filtered daily in the glomeruli of a normal healthy adult. Typically, all of this glucose is reabsorbed with <1% being excreted in the urine. The transport of glucose from the tubule into the tubular epithelial cells is accomplished by sodium-glucose co-transporters (SGLTs). SGLTs encompass a family of membrane proteins that are responsible for the transport of glucose, amino acids, vitamins, ions and osmolytes across the brush-border membrane of proximal renal tubules as well as the intestinal epithelium. SGLT2 is a high-capacity, low-affinity transporter expressed chiefly in the kidney. It accounts for approximately 90% of glucose reabsorption in the kidney and has thus become the focus of a great deal of interest in the field of diabetes mellitus.[9]

RENAL GLUCONEOGENESIS IN THE POSTABSORPTIVE STATE:

In the fasting state in healthy individuals, the kidneys contribute about 20% to 25% of the glucose released into the circulation via gluconeogenesis (15–55 g per day), with the liver responsible for the remainder via both glycogenolysis and gluconeogenes and Renal gluconeogenesis occurs predominantly within proximal tubule cells in the renal cortex, and is chiefly regulated by insulin and catecholamines (eg, adrenaline). Insulin reduces renal gluconeogenesis directly, and also reduces the availability of gluconeogenic substrates, such as lactate, glutamine, and glycerol, thus reducing glucose release into the circulation. Adrenaline stimulates renal gluconeogenesis and, stimulates renal glucose release,

inhibits insulin secretion, increases the supply of gluconeogenic substrates, and reduces renal glucose uptake.

In patients with T2DM, both renal and hepatic glucose release are increased as a result of increased gluconeogenesis. The relative increase in renal gluconeogenesis is thought to be substantially greater than in hepatic gluconeogenesis (300% vs 30%). Renal glycogenolysis is minimal in healthy individuals but may play a role in increased renal glucose release in patients with T2DM, due to accumulation of glycogen in diabetic kidneys.[10]

RENAL GLUCOSE RELEASE IN THE POSTPRANDIAL STATE:

Renal gluconeogenesis increases during the postprandial state relative to the post absorptive state. Studies using stable isotopes to estimate renal glucose balance have shown renal glucose release increases more than 2-fold during the 4.5-hour postprandial period. It is thought that this increase in renal glucose release allows for repletion of hepatic glycogen stores by permitting suppression of hepatic glucose release. The mechanisms for this are not known, but may include the postprandial increases in lactate and amino acids that are precursors for gluconeogenesis, as well as an increase in sympathetic nervous system activity. Indeed, renal glucose production accounts for 60% of endogenous glucose release during the postprandial period (4–6 hours after meals).

The increase in glucose release over the 4.5-hour postprandial period has been shown to be roughly 30% higher (100 g vs 70 g) in patients with T2DM compared with healthy individuals, primarily due to increased endogenous glucose release. It is estimated that 40% of the increase in endogenous glucose release occurs via the kidney. Renal glucose release is regulated by insulin; thus, as insulin

resistance increases, suppression of renal glucose release decreases, increase in renal glucose reabsorption due to upregulation of renal glucose transporters (GLUTs).[11]

RENAL GLUCOSE TRANSPORT:

The kidneys play a key role in glucose conservation, filtering 160 to 180 g of glucose per day in healthy individuals, which is all reabsorbed within the proximal tubules and Glucose reabsorption occurs via both sodium glucose co-transporters (SGLTs) and GLUTs. The energy for SGLT-mediated active transport of glucose across the cell membrane is derived from the sodium electrochemical potential gradient. This is maintained by the transport of intracellular sodium ions into the blood via sodium-potassium adenosine triphosphatase (ATPase) pumps situated in the basolateral membrane. GLUTs bind glucose, inducing a conformational change, and glucose is passively transported across the cell membrane from the intracellular compartment into the plasma.[12]

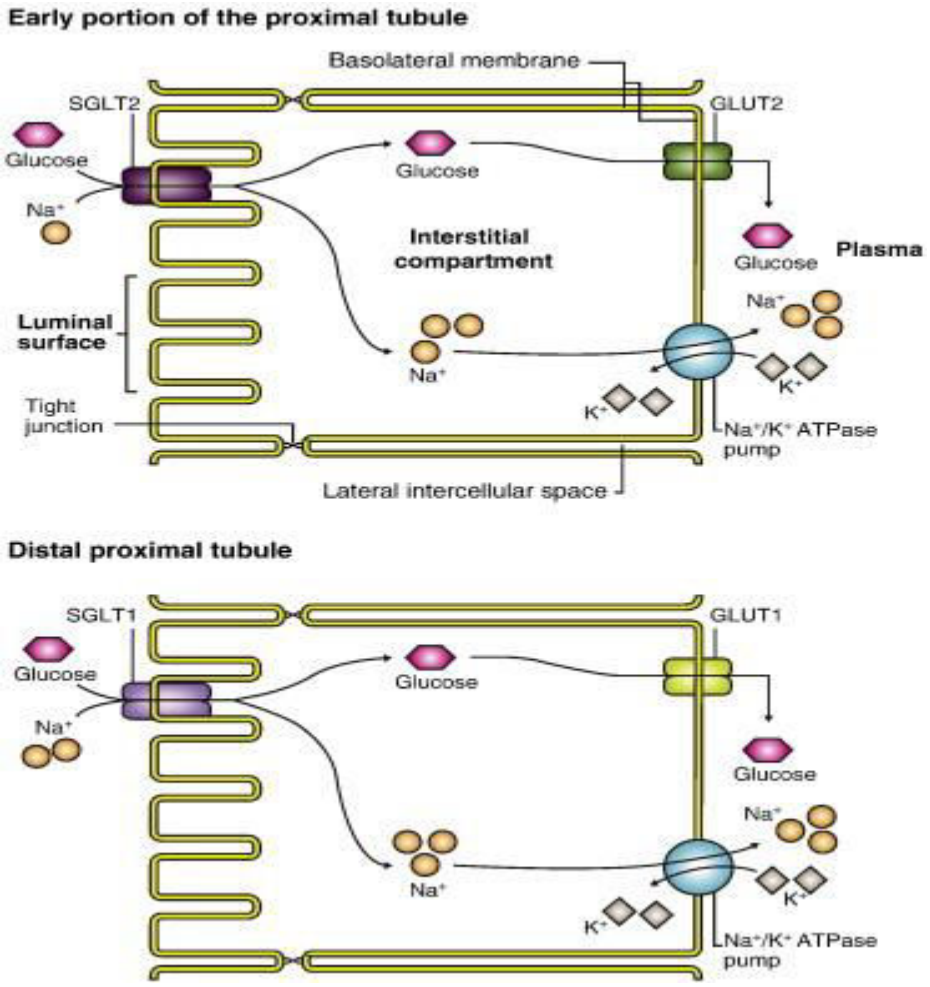

FIGURE 3: EARLY PORTION OF THE PROXIMAL TUBULE AND DISTAL PROXIMAL TUBLE.

Within the proximal renal tubule, 2 key subtypes of SGLT and GLUT are responsible for glucose reabsorption and are expressed at the luminal brush border and the basolateral membrane of the epithelial cells, respectively.

SGLT2 is a high-capacity, low-affinity co-transporter that is responsible for the majority of renal glucose reabsorption, coupling the active transport of sodium and glucose in a 1:1 ratio within the early proximal tubule. Glucose is then reabsorbed into the circulation via GLUT2. Any remaining glucose

is reabsorbed by SGLT1, a high-affinity transporter expressed within the distal proximal tubule (sodium : glucose ratio of 2:1) and then reabsorbed into the blood via GLUT1.

RENAL GLUCOSE REABSORPTION AND THE RENAL THRESHOLD FOR GLUCOSE EXCRETION:

The physiologic relationship between plasma glucose concentration and renal glucose flux (i.e., filtration, reabsorption, and excretion) has typically been described as a threshold-type relationship .The amount of glucose filtered by the kidneys increases in a linear manner with increasing plasma glucose concentration and decreases with declining glomerular filtration rate (GFR); renal glucose reabsorption increases linearly until a certain concentration of plasma glucose is present. However, there is a distinct deviation from this linear relationship as the renal capacity to reabsorb glucose nears saturation that is thought to be due to variability in the maximal reabsorptive capacity between individual nephrons.[13]

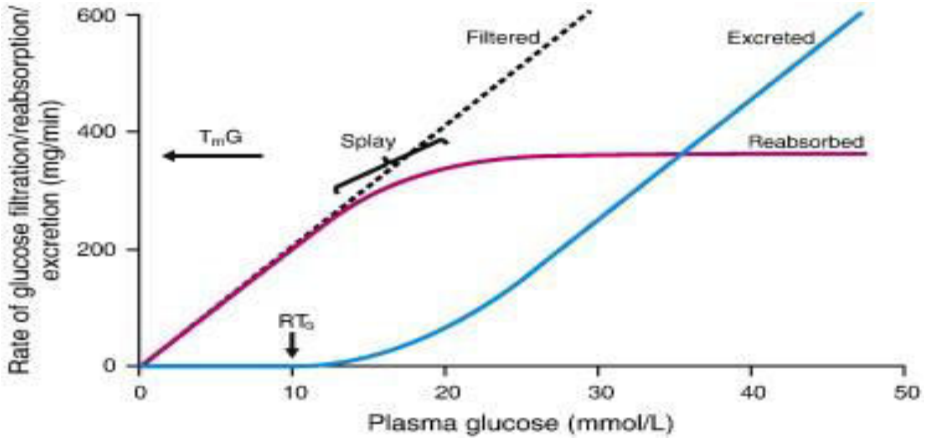

FIGURE 4: T_MG, TUBULAR MAXIMUM GLUCOSE REABSORPTIVE CAPACITY; RT_G, RENAL THRESHOLD FOR GLUCOSE EXCRETION.

Under normal conditions in healthy individuals, nearly all filtered glucose is reabsorbed in the renal tubules. However, when the filtered glucose load exceeds the tubular maximum glucose reabsorptive capacity excess glucose is excreted in the urine .The renal threshold for glucose excretion (RT_G) is the plasma glucose concentration at which T_mG is exceeded; below this concentration, glucosuria is minimal. whereas, in patients with T2DM, RT_G is elevated. While studies evaluating RT_G in patients with T2DM suggest some inter individual variability, many patients demonstrate elevated values above the normal range, with values ranging from 112 to 240 mg/dL (6.2–13.3 mmol/L).

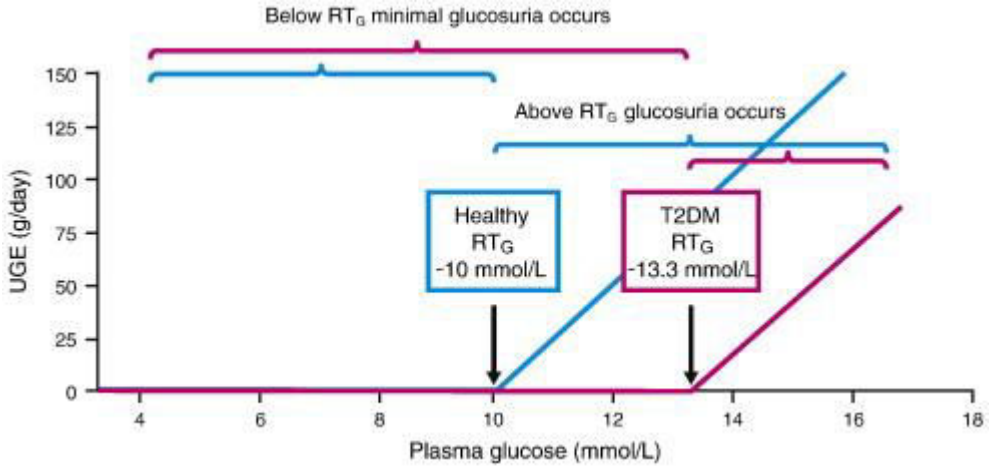

FIGURE 5: LINEAR RELATIONSHIP BETWEEN UGE AND PLASMA GLUCOSE CONCENTRATION IN HEALTHY INDIVIDUALS AND PATIENTS WITH T2DM.

T_mG may also be elevated in individuals with diabetes, contributing to the worsening of hyperglycemia. Increased tubular reabsorption may be due to an increase in GLUT expression or activity, with up regulation of SGLT2 or GLUT2 being possible mechanisms for the increase in glucose reabsorption.. In a hyperglycemic culture environment, both SGLT2 and GLUT2 mRNA levels and glucose transport were significantly higher in the T2DM group versus controls. The increases in tubular reabsorption in individuals with T2DM lead to an increase in glucose flux into the blood, resulting in an exacerbation of hyperglycemia. Based on observations that mean RT_G is approximately 40 mg/dL (2.2 mmol/L) higher in patients with T2DM than the commonly reported values of 180 to 200 mg/dL (10–11 mmol/L) in healthy individuals and using a mean GFR of 100 mL/min, calculations suggest that elevated RT_G leads to an average of approximately 50 to 70 mg/min of additional glucose reabsorbed into the circulation when plasma glucose is above the RT_G, relative to glucose reabsorption

if RT_G was not increased. For comparison, elevated hepatic glucose production is estimated to contribute approximately 24 mg/min of additional glucose in a 100-kg patient with T2DM. Thus, both the kidney and the liver substantially contribute to the hyperglycemia seen in patients with T2DM. However, it should be noted that additional renal glucose reabsorption may be substantially lower in patients with impaired renal function, since their GFR will be lower than 100 mL/min.[14]

GENETIC DEFECTS IN RENAL GLUCOSE TRANSPORT:

Specific mutations in SGLT genes can result in naturally occurring glucosuria. Glucose-galactose malabsorption (GGM) is a rare condition caused by mutations of SGLT1, leading to malabsorption of these sugars due to failure of the gastrointestinal epithelial cells to accumulate sugar across the brush border membrane. This results in gastrointestinal symptoms such as diarrhea and dehydration presenting in the neonatal period; treatment requires removal of glucose and galactose (which is also transported by SGLT1) from the diet. Glucosuria in individuals with GGM is typically absent or mild, consistent with the minor role of SGLT1 in renal glucose reabsorption.

Familial renal glucosuria (FRG) is a rare autosomal recessive renal disorder that results from mutations in the *SLC5A2* gene (coding for SGLT2) in the majority of cases. Heterozygous FRG is characterized by glucosuria of ~ 0 to 10 g/day at normal plasma glucose concentrations in the absence of renal tubular dysfunction. FRG is generally asymptomatic and considered to be a benign condition. Homozygous FRG may result in glucosuria of up to 200 g/day, but is rarely described.

SGLT2 INHIBITION IN T1DM:

SGLT2 inhibition was associated with improvements in glycemic control, reductions in daily insulin doses, and reductions in body weight.

SGLT2 inhibition for the treatment of T2DM:

Inhibition of SGLT2 has emerged as a focus for the development of novel treatments for patients with T2DM. These therapies reduce blood glucose concentrations by lowering the RT_G and inducing glucosuria in an insulin-independent manner. Two SGLT2 inhibitors, canagliflozin and dapagliflozin, are currently approved for use in patients with T2DM in over 30 countries worldwide.

The importance of the kidney in glucose homeostasis has been recognized for many years. Recent observations indicating a greater role of renal glucose metabolism in various physiologic and pathologic conditions have rekindled the interest in renal glucose handling as a potential target for the treatment of diabetes. The enormous capacity of the proximal tubular cells to reabsorb the filtered glucose load entirely, utilizing the sodium-glucose co-transporter system (primarily SGLT-2), became the focus of attention. In general, a 6-month period of therapy with SGLT-2 inhibitors is followed by a mean urinary glucose excretion rate of ~80 g/day accompanied by a decline in fasting and postprandial glucose with average decreases in HgA1C ~1.0%. Concomitant body weight loss and drop in blood pressure also have been reported. In contrast, transient polyuria, thirst with dehydration and occasional hypotension have been described early in the treatment. In addition, a significant increase in the occurrence of uro-genital infections, particularly in women has been documented with the use of SGLT-2 inhibitors.[16]

Interestingly, attention is once again focused on the kidney, not only as an organ that may be adversely affected by diabetes, but also as an important player in glucose homeostasis and a potential target for the treatment of hyperglycemia in type 2 diabetes. the role of the kidney in normal glucose homeostasis and in type 2 diabetes and how inhibition of renal glucose reabsorption may become a novel treatment option in patients with type 2 diabetes.

Type 2 diabetes is a progressive disease. As such, patients with type 2 diabetes can have various levels of hyperglycemia, and therapy should be individualized, taking into account the duration of disease, life expectancy, presence of complications and comorbidities, and risk for severe hypoglycemia. For example, patients with an A1C $\leq$ 7.5% may be able to reach glycemic goals with monotherapy. In contrast, patients with an A1C of 7.6–9.0% will likely require two diabetes medications, and patients with an A1C > 9% will probably require two diabetes medications and insulin.

SGLT2 inhibitors block the reabsorption of filtered glucose leading to glucosuria. the glucosuria associated with SGLT2 inhibition is associated with caloric loss, thus providing a potential benefit of weight loss.SGLT2 inhibition cause glucose elevation in the urine lead to urinary tract and genital infections, electrolyte imbalances and increased urinary frequency.[17]

SGLT2 INHIBITORS AND GLOMERULAR HYPERFILTRATION:

The two most important pathophysiological mechanisms leading to renal hyperfiltration in diabetes are glomerular hemodynamic abnormalities due to neurohormonal activation and tubular factors. The hemodynamic/neurohormonal hypothesis is based on changes in afferent and efferent arteriolar tone, resulting in

glomerular hyperfiltration, mostly due to RAAS activation. The tubular hypothesis is based on the fact that hyperglycemia causes an increase in proximal tubule glucose filtered load in diabetes. This results in over activity of SGLT2 and SGLT1 and consequent increased tubular reabsorption of glucose and sodium and downstream activation of the tubuloglomerular feedback system . This increased proximal sodium reabsorption leads to decreased sodium delivery to and transport in the cells of the macula densa, with consequent reduction in ATP breakdown and adenosine production. Adenosine is a strong vasoconstrictor, and its reduction causes vasodilation of the afferent arteriole and thus hyperfiltration

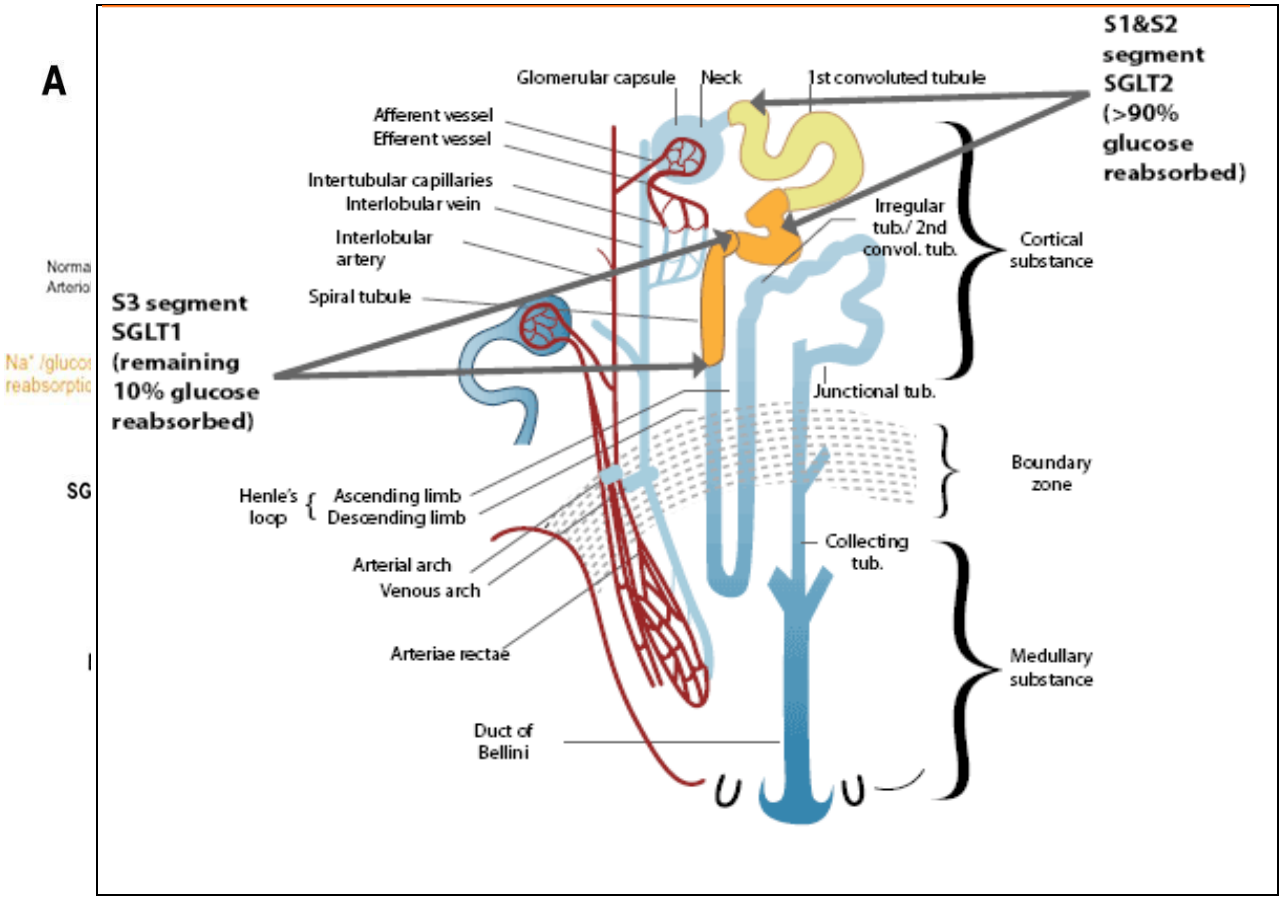

FIGURE 6:TUBULOGLOMERULAR FEEDBACK SYSTEM

SGLT-2 is primarily expressed in the kidney on the epithelial cells lining the first segment of the proximal convoluted tubule. It is the major transport protein that promotes reabsorption from the glomerular filtration glucose back into circulation and is responsible for approximately 90% of the kidney's glucose reabsorption.

By inhibiting SGLT-2, medications of the gliflozin class 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 (glucosuria).

Interestingly, attention is once again focused on the kidney, not only as an organ that may be adversely affected by diabetes, but also as an important player in glucose homeostasis and a potential target for the treatment of hyperglycemia in type 2 diabetes.[18]

SGLT2 expression was localized to the brush border of the early proximal tubule in the human kidney and was found upregulated in genetic murine models of type 1 and 2 diabetes. SGLT2 may functionally interact with the Na/H exchanger NHE3 in the proximal tubule. SGLT1-mediated reabsorption explains the fractional renal glucose reabsorption of 40-50% during SGLT2 inhibition. SGLT2 is expressed on pancreatic alfa cells where its inhibition induces glucagon secretion. SGLT2 inhibition lowers glomerular filtration rate in hyperfiltering diabetic patients consistent with the tubular hypothesis of diabetic hyperfiltration. New data indicate a potential of SGLT2 inhibition for renal medullary hypoxia and ketoacidosis, but also for blood glucose effect-dependent and independent nephroprotective actions, renal gluconeogenesis inhibition, reduction in cardiovascular mortality, and cancer therapy.

Because of its role in glucose homeostasis, the kidney has become a target of drug therapy for the treatment of type 2 diabetes. Increasing the excretion of glucose by inhibition of SGLT2, the transporter responsible for the majority of glucose reabsorption, improves glycemic control in patients with type 2 diabetes.

In human tubular epithelial cells grown from urines of patients with type 2 diabetes , there is an increase in the expression and glucose-transport capacity of SGLT2 compared with those from control subjects without diabetes. Thus, SGLT2 inhibition should result in an increased delivery of sodium to the macula densa, a consequent increase in adenosine release, resulting in vasoconstriction of the afferent arteriole leading to a reduction in renal plasma flow and GFR.

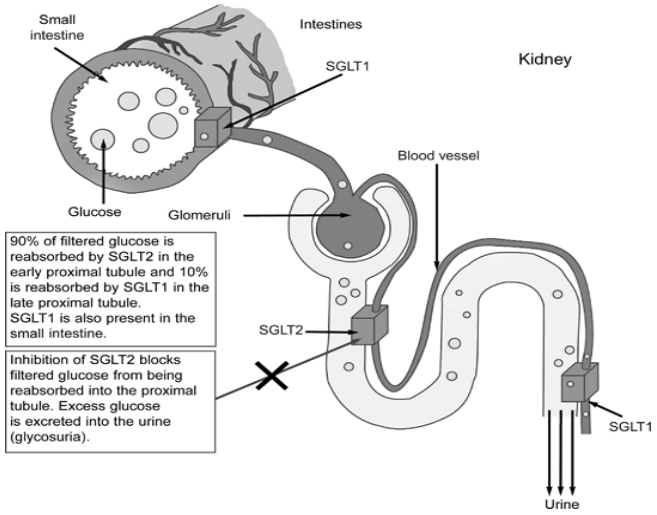

FIGURE 7: SODIUM GLUCOSE CO TRANSPORTER 2 INHIBITORS: AN EMERGING NEW CLASS OF ORAL ANTIDIABETIC DRUG.

The most important structural changes in type 1 diabetes occur in the glomeruli, with thickening of the glomerular basement membrane, mesangial expansion, and podocyte injury; in the presence of more advanced DN, however, there are also important changes in the tubules and interstitium with tubular atrophy and interstitial fibrosis and inflammation . In contrast, among patients with type 2 diabetes and microalbuminuria or macroalbuminuria and preserved renal function , a substantial proportion (~40%) has advanced tubulo-interstitial lesions despite only very mild glomerular lesions. These lesions include thickening and reduplication of tubular basement membrane, tubular atrophy, interstitial fibrosis, and chronic inflammation. When proximal tubular cells are grown in high-glucose conditions, there is an increased secretion of inflammatory molecules and profibrotic cytokines . In vivo, this leads to activation of inflammatory pathways, recruitment of macrophages, and further tubular damage and interstitial fibrosis. transforming growth factor-β probably plays a key role, promoting fibrosis and epithelial-to-mesenchymal transformation . The increase in glucose trafficking through the proximal tubular cells, an increased transport of glucose by SGLT2, could promote inflammation and fibrosis. Thus, it is tempting to hypothesize that in patients with type 2 diabetes and tubulointerstitial lesions SGLT2 inhibitors might be particularly useful in reducing tubulointerstitial fibrosis and inflammation.[19]

SGLT2 INHIBITORS AND RENAL FUNCTION IN CLINICAL STUDIES:

The changes in GFR during SGLT2 inhibition are similar in patients with normal renal function and in those with CKD. The time course of changes in renal function is typically characterized by a rapid decline in GFR during the first weeks of treatment, followed by a progressive recovery that is faster and more

evident in patients with normal renal function at baseline. In addition to the effects on GFR, SGLT2 inhibitors also influence albuminuria. Additional recent data also support the concept that SGLT2 inhibitors reduce albuminuria.

By inhibiting SGLT-2, medications of the gliflozin class 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.

Interestingly, attention is once again focused on the kidney, not only as an organ that may be adversely affected by diabetes, but also as an important player in glucose homeostasis and a potential target for the treatment of hyperglycemia in type 2 diabetes.

SGLT2 expression was localized to the brush border of the early proximal tubule in the human kidney and was found up regulated in genetic murine models of type 1 and 2 diabetes. SGLT2 may functionally interact with the Na/H exchanger NHE3 in the proximal tubule. SGLT1-mediated reabsorption explains the fractional renal glucose reabsorption of 40-50% during SGLT2 inhibition. SGLT2 is expressed on pancreatic alfa cells where its inhibition induces glucagon secretion. SGLT2 inhibition lowers glomerular filtration rate in hyperfiltering diabetic patients .New data indicate a potential of SGLT2 inhibition for renal medullary hypoxia and ketoacidosis, but also for blood glucose effect-dependent and independent nephroprotective actions, renal gluconeogenesis inhibition, reduction in cardiovascular mortality, and cancer therapy.[20]

GLUCOSE-LOWERING EFFICACY OF SGLT2 INHIBITORS IN PATIENTS WITH CKD:

The efficacy of SGLT2 inhibitors in reducing plasma glucose is expected to be decreased with decreasing renal function. Since glucose-lowering agents for patients with CKD stages 3 and 4 are limited and frequently require dose adjustments, the identification of the cut off of estimated GFR (eGFR) below which clinically significant reductions in plasma glucose cannot be achieved with SGLT2 inhibitors is crucial. On the basis of the studies performed so far in patients with CKD, these drugs should not be started in patients with eGFR <60 mL/min/1.73 m^2 and should be stopped when eGFR is <45 mL/min/1.73 m^2.

The kidney is the organ that filters about 45 gallons of blood each day. Most of the glucose in this blood is reabsorbed by the kidneys by a protein called Sodium-Glucose co transporter-2 (SGLT2). Here SGLTs are responsible for mediating glucose reabsorption in the kidneys. The inhibition of Sodium-Glucose co transporter-2, the re-absorption of the glucose back in to systemic circulation is by passed and the unabsorbed glucose is excreted through urine.[21]

The kidneys play an important role in regulating glucose homeostasis through gluconeogenesis, glucose uptake and utilization, and glucose reabsorption in the proximal renal tubule. The RT_G is the plasma glucose concentration at which glucose reabsorption capacity is exceeded and glucosuria occurs. The RT_G has been estimated to be between 180 and 200 mg/dL (10–11 mmol/L) in healthy individuals; this is increased in patients with T2DM. The resulting increase in glucose reabsorption is thought to contribute to the maintenance of hyperglycemia. Type 2 diabetes is a progressive disease. As such, patients with type 2 diabetes can have various levels of hyperglycemia, and therapy should be individualized, taking

into account the duration of disease, life expectancy, presence of complications and co-morbidities, and risk for severe hypoglycaemia.

Because of its role in glucose homeostasis, the kidney has become a target of drug therapy for the treatment of type 2 diabetes. Increasing the excretion of glucose by inhibition of SGLT2, the transporter responsible for the majority of glucose reabsorption, improves glycemic control in patients with type 2 diabetes.

In the kidney, glucose is freely filtered at the glomerulus and is reabsorbed via active transport mechanisms in the proximal convoluted tubule. Two sodium-glucose co-transporters are responsible for glucose reabsorption: SGLT1 and SGLT2. SGLT1, which is also found in the gut and other tissues, accounts for about 10% of reabsorption. SGLT2, expressed exclusively in the S1 segment of the proximal tubule, accounts for about 90% of reabsorption The concentration gradient that drives the action of these transporters is driven by the Na+/ATPase pump and by transport back into the blood via the GLUT2 glucose transporter . This suggests that the most promising target for drug development is the SGLT2 transporter, both because it is responsible for most glucose reabsorption and because of its exclusive localization to the kidney.[23]

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a new class of diabetic medications indicated only for the treatment of type 2 diabetes. In conjunction with exercise and a healthy diet, they can improve glycemic control. SGLT2 is a protein in humans that facilitates glucose reabsorption in the kidney. SGLT2 inhibitors block the reabsorption of glucose in the kidney, increase glucose excretion, and lower blood glucose levels.

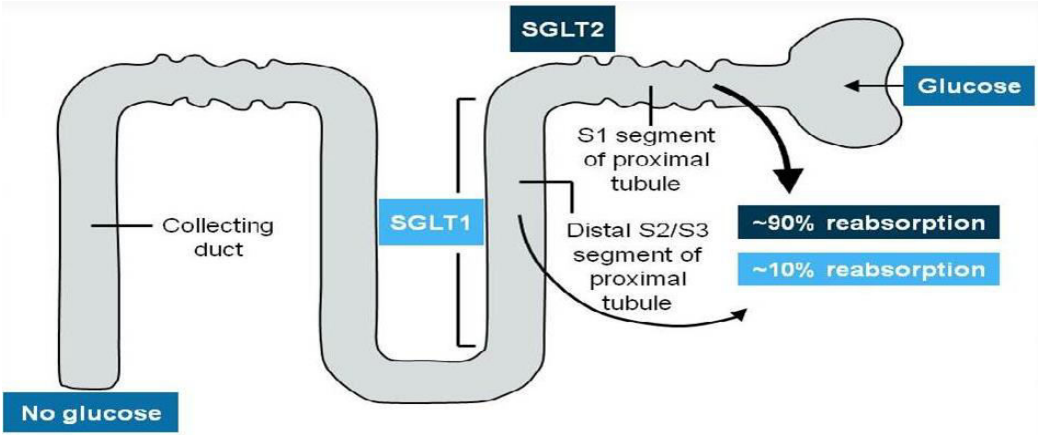

FIGURE 8: SGLT-2 IS PRIMARILY EXPRESSED IN THE KIDNEY

SGLT-2 is primarily expressed in the kidney on the epithelial cells lining the first segment of the proximal convoluted tubule. It is the major transport protein that promotes reabsorption from the glomerular filtration glucose back into circulation and is responsible for approximately 90% of the kidney's glucose reabsorption.

The mechanism of action of SGLT2 inhibitors is independent of insulin secretion or action and complementary to existing diabetes medications, they may be effective across all stages of the disease when used as monotherapy or in combination with metformin, sulfonylureas, thiazolidinediones, or insulin. Additional effects that have been reported in some trials of SGLT2 inhibitors include weight loss and blood pressure reduction, both of which are beneficial in this patient population.

SGLTs are responsible for mediating glucose reabsorption in the kidneys, as well as in the gut and the heart. SGLT-2 is primarily expressed in the kidney on the epithelial cells lining the first segment of the proximal convoluted tubule. It is the major transport protein that promotes reabsorption from the

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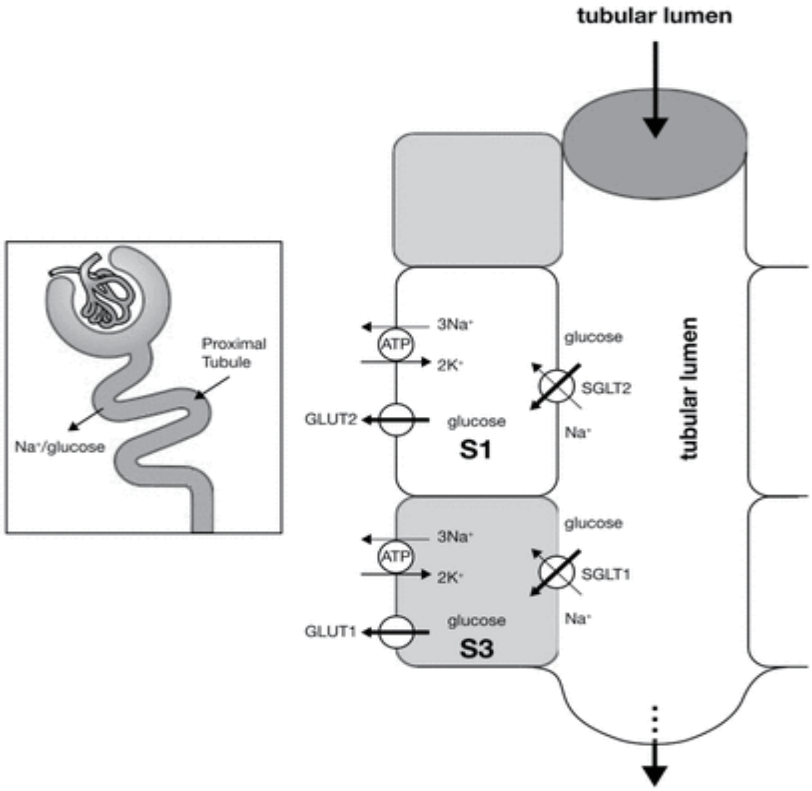

FIGURE 9: GLUCOSE REABSORPTION IN THE KIDNEY

Sodium and glucose are co-transported by the SGLT-2 protein into the tubular epithelial cells across the brush-border membrane of the proximal convoluted tubule. 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 endothelial cells into the interstitial glucose transporter protein.

In humans, SGLT2 inhibition was recently shown to reduce hyperfiltration in normotensive, normoalbuminuric patients with type 1 diabetes. In clinical trials of type 2 diabetes, SGLT2 is associated with significant renal effects, including modest, acute declines in estimated glomerular filtration rate followed by the maintenance of stable renal function, and reduced albuminuria.

hyperfiltration has been used as a surrogate marker for increased intraglomerular pressure in patients with diabetes mellitus. Previous human investigation examining the pathogenesis of hyperfiltration has focused on the role of neurohormones such as the renin-angiotensin-aldosterone system (RAAS). Unfortunately, RAAS blockade does not completely attenuate hyperfiltration or diabetic kidney injury. More recent work has therefore investigated the contribution of renal tubular factors, including the sodium-glucose cotransporter, to the hyperfiltration state,

Moreover, Gilbert highlights the initial drop in eGFR in the treatment group. In the following 100 weeks, eGFR slowly fell in the placebo group, while it stabilized and even rose slightly in the treatment group. He noted that the initial fall in eGFR in the treatment group could be related to mild volume depletion, while the longer-term results could suggest possible nephroprotective effects in SGLT2 inhibitors similar to that seen with ACE inhibitors.[25]

Increasing the excretion of glucose by inhibiting SGLT2 has a number of potential benefits. SGLT2 inhibitors, by increasing the excretion of glucose, decrease plasma glucose concentrations and have the additional benefit of reducing

body weight. Moreover, because the mechanism of action of SGLT2 inhibitors does not depend on the presence of insulin, the efficacy of SGLT2 inhibitors would not be primarily affected by the magnitude of insulin resistance or impairment of pancreatic β-cell function that accompanies type 2 diabetes progression. In addition, the risk of major hypoglycemic events is low with SGLT2 inhibitors because they do not impair normal endogenous glucose production in response to hypoglycemia and do not stimulate insulin release, suggesting that SGLT2 inhibitors may preserve the hypoglycemia counter regulatory response of glucagon-mediated glucose production. Finally, there is a potential for combination therapy with other diabetes agents, including insulin, to improve glycemic control.

As discussed below, results from clinical trials have confirmed that SGLT2 inhibition improves glycemic control, reduces body weight, and is effective when used as monotherapy or as add-on therapy to commonly used diabetes medications in patients with type 2 diabetes, both in drug-naive patients with a short duration of disease and in those with a long history of type 2 diabetes who are receiving insulin therapy. However, because SGLT2 inhibitors depend on the filtration and delivery of glucose to the proximal tubule, they are not effective in patients with moderate to severe renal impairment. Furthermore, continual excretion of urine with high glucose concentrations may predispose individuals to genital and urinary tract infections.

Sodium and glucose are co-transported by the SGLT-2 protein into the tubular epithelial cells across the brush-border membrane of the proximal convoluted tubule. 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 endothelial cells into the interstitial glucose transporter protein.

Since sodium glucose co transporter 2 (SGLT2) inhibitors rely on the glomerulus to filter urine, their ability to lower blood glucose is limited in patients with type 2 diabetes who have chronic kidney disease (CKD). On the other hand, there is some research to suggest that use of SGLT2 inhibitors may confer some degree of nephroprotection.SGLT2 inhibitors could slow the progression of diabetic nephropathy, by decreasing glomerular hyper filtration, hyperglycemia-related tubular growth, kidney hypertrophy, and inflammation and fibrosis implicated in the development of diabetic nephropathy.

Nephro protective potential of SGLT2 inhibitors suppress renal hyper filtration independent of their effect on blood glucose levels. Conversely, the ability of SGLT2 inhibitors to reduce kidney growth and injury seems to depend on their glycemia-lowering effects. Inflammatory and fibrotic responses resulting from high glucose levels could also be decreased by SGLT2 inhibition, likely by blocking glucose entry into the cell.[26]

ADVANTAGES AND DISADVANTAGES OF USING SGLT2 INHIBITORS TO IMPROVE GLYCEMIC CONTROL IN PATIENTS WITH T2D:

ADVANTAGES:

•Significant improvements in glycemic control sustained over time.
•Sustained, clinically meaningful reductions in body weight.
•Sustained, clinically meaningful reductions in systolic blood pressure.
•Insulin-independent mechanism of action.

•Improvements in insulin sensitivity and β-cell function.

•Generally safe and well tolerated.

•Low risk of hypoglycemia.

•Can be used as mono therapy or combined with other AHAs, including insulin.

DISADVANTAGES:

•Increased incidence of mild to moderate genital mycotic infections and UTIs vs comparators.

•Higher incidence of osmotic diuresis related AEs vs comparators.

•Increased incidence of volume depletion– related AEs in elderly patients and in patients with eGFR < 60 mL/min/1.73 m^2

•Increased LDL-C level.[27]

As the prevalence of T2DM grows, selecting appropriate antihyperglycemic agents to manage T2DM will continue to challenge healthcare providers. Overall, it is likely that SGLT2 inhibitors will prove to be valuable new anti hyperglycemic agents for the treatment of patients with T2DM.

Selective sodium-glucose transporter-2 (SGLT-2) inhibitors are a class of oral hypoglycemics used in patients with diabetes mellitus type 2. These agents lower the renal glucose threshold, resulting in an increased amount of glucose being excreted in the urine.

SGLT2 inhibitors inhibit the SGLT2 in the proximal nephron, subsequently reducing the reabsorption of filtered glucose. Excretion of glucose in the urine is increased by up to 80g per day . These agents provide modest weight

loss as the result of increased loss of urinary glucose and reduction in blood pressure by means of osmotic diuresis effects .An additional advantage of SGLT2 inhibitors is that these agents are effective at all stages of type 2 diabetes mellitus (T2DM) . When therapy is advanced to combination basal/bolus insulin regimens, physicians may discontinue agents such as sulfonylureas and GLP-2 receptor agonists. SGLT inhibitors can be utilized as adjuantive therapy to improve glucose control and reduce the amount of insulin needed.

All of the SGLT2 inhibitors are available as an oral tablet formulation. The oral bioavailability of the SGLT2 inhibitors range from 60-78% and achieves maximum concentration 1-2 hours after administration. The elimination half-life of this class of medication ranges from 10.2-13.1 hours and have a once-daily dosing. Drug metabolism is primarily through glucuronidation by the liver and excretion of the drug is mainly by means of the urinary and fecal route. Since the SGLT2 inhibitors reduce the reabsorption of glucose in the kidney and reduce filtration rates, patients with renal impairment will require additional monitoring and/or dose adjustment. The risk of hypoglycemia is low when a SGLT2 inhibitor is administered as monotherapy. In combination therapy, the SGLT2 drug class may enhance the hypoglycemic effects with insulin and insulin secretagogues such as sulfonylureas. Prescribers should consider lowering the dose of insulin and monitoring for signs and symptoms of hypoglycemia when initiating SGLT2 adjunctive therapy.[28]

Genitourinary infections and polyuria were the most commonly reported adverse events and patients presenting with symptoms should be evaluated. Hypotension, dizziness, and dose-related increase in LDL cholesterol have also been reported. Fractures are rare, but have occurred in susceptible

patients. Due to the renal mechanism of action of SGLT2 inhibitors, clinicians need to assess renal function. As this class of medication is contraindicated in patients with severe renal function including eGFR <30mL/min/1.73m [2], end-stage renal disease or on dialysis. Bladder cancer has been reported in patients treated with SGLT2 inhibitors in clinical trials, but there is insufficient data to determine if these cases were related to the effects of SGLT2 medications. Case reports of ketoacidosis have been identified in post-marketing surveillance, and the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) have found in their review of these cases that the incidence of ketoacidosis to be infrequent. If ketoacidosis is suspected or if patient is at risk for ketoacidosis. the SGLT2 agent should be discontinued immediately.[29]

MECHANISM OF ACTION:

Functioning of SGLTs are dependent on the Na+/K+ ATPase pump on the baso-lateral membrane which uses ATP to move sodium ions outward into the blood, while bringing in potassium ions. This creates a downhill sodium ion gradient inside the cell in comparison to both the blood and the tubule/ gastric lumen. The SGLT proteins use the energy from this downhill sodium ion gradient created by the ATPase pump to transport glucose across the apical membrane against an uphill glucose gradient. Therefore, these co-transporters are an example of secondary active transport. Since both sodium ions and glucose are transported in the same direction across the membrane, they are also called symporters.

Around 180 grams of glucose is filtered by the renal tubules per day. Virtually all of this is re-absorbed from the proximal tubules, and re-enters the circulation. 90% of this re-absorption is SGLT2 mediated and the remaining by SGLT1. Inhibition of these SGLT2 channels by SGLT2 inhibitors leads to

persistent increased glycosuria, and lowering of blood glucose which leads to decreased glucotoxicity, decreased insulin resistance, and an improvement in insulin secretion. The advantage of this group of drugs is that their action is independent of residual beta cell function. This means that SGLT2 inhibitors may find a place in the management of T1D as well. Interestingly, in a follow-up study, it has been demonstrated that use of SGLT2 inhibitor, LX4211 (300 mg) resulted in significantly increased GLP-1 & peptide YY levels, probably by delaying SGLT1-mediated intestinal glucose absorption. Hence SGLT2 inhibitors exhibit some incretin-based effects as well.[21]

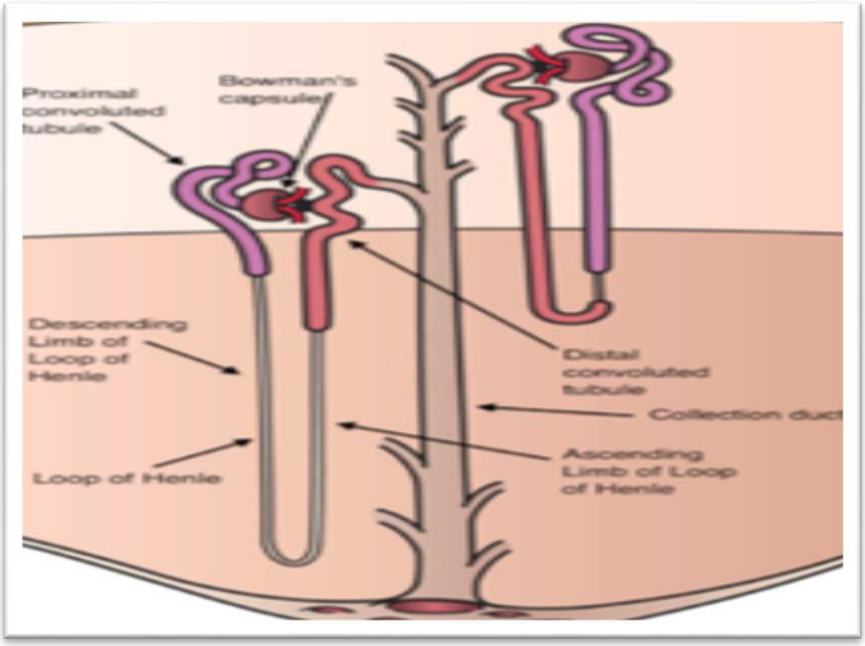

FIGURE 10:KIDNEY NEPHRON

SGLTs are responsible for mediating glucose reabsorption in the kidneys, as well as in the gut and the heart. SGLT-2 is primarily expressed in the kidney on the epithelial cells lining the first segment of the proximal convoluted

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Sodium and glucose are co-transported by the SGLT-2 protein into the tubular epithelial cells across the brush-border membrane of the proximal convoluted tubule. 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 endothelial cells into the interstitial glucose transporter protein.[30]

PATHOPHYSIOLOGY OF TYPE 2 DIABETES:

Type 2 diabetes is characterized by resistance to the glucose-lowering effects and some other effects of insulin and a progressive failure of pancreatic beta-cell function.. This can be seen with regard to the genetics of the condition; there is a high degree of heritability (about 70% concordance in identical twins), but it is likely that many genes contribute. Recent genome-wide association studies have identified TCF7L2, which may relate to insulin secretion, and FTO -- variants of which are associated with a slight increase in body fat as being potentially important. Rare single-gene defects result in maturity-onset diabetes of the young (MODY), which can manifest as a pancreatic defect (eg, with a defect in the pancreatic glucose sensor glucokinase, MODY 2) or in hepatic and pancreatic function (hepatocyte nuclear factor [HNF]-1 alpha and HNF-4 genes, MODY 3, and MODY 4). Some cases are associated with autoimmunity and may in fact be a

slow-onset form of type 1 diabetes (late-onset autoimmune diabetes [LADA]). Hence, it is unlikely that any single pathophysiologic mechanism will eventually explain all cases of type 2 diabetes or suggest a therapeutic advance that will be suitable for all patients with the condition.[31]

THE ROLE OF THE KIDNEY IN NORMAL GLUCOSE HOMEOSTASIS:

The kidney plays a vital role in the normal control of blood glucose, mainly because glucose in the blood is freely filtered by the glomerulus and has to be reabsorbed. The kidney also contributes to gluconeogenesis, and can make up to about 5% to 10% of overall glucose production in humans. In healthy individuals, the kidneys filter about 100 mg/minute of glucose; this amounts to 144 g/24 hours. Nearly 100% of this glucose is reabsorbed, mostly in the proximal renal tubules. At a threshold of about 8-10 mmol/L (180 mg/dL), the capacity to reabsorb glucose is exceeded and glucosuria develops in proportion to the level of blood glucose. This renal threshold for glucose there is some variation from the idealized curve and what is observed from actual measurements in humans. This "splay" is thought to occur as a result of the differences between the filtration rate of individual nephrons and the fact that the transport system, like all biological systems, is not 100% perfect at reabsorbing all of the filtered glucose.

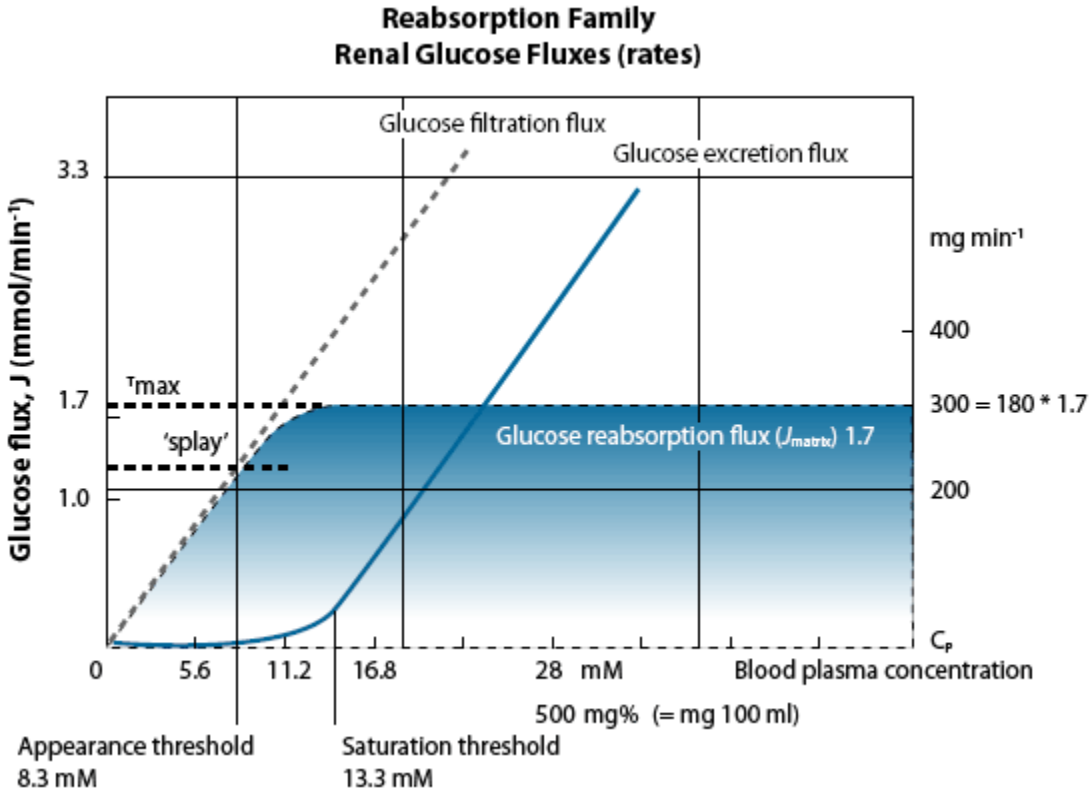


FIGURE 11: RENAL GLUCOSE FLUXES

In normal glucose reabsorption threshold occurs at 8.3 mmol/L plasma glucose and is saturated at around 13.3 mmol/L. Glucose excretion then increases linearly. Splay is thought to represent a slight variation between thresholds of individual nephrons.

Glucosuria thus occurs in the presence of hyperglycemia, and has been used to demonstrate the presence of diabetes and monitor glycemic control long before the routine measurement of capillary blood glucose became possible.[32]

MECHANISMS RESPONSIBLE FOR RENAL GLUCOSE REABSORPTION:

Most glucose reabsorption occurs in the proximal tubules of the nephron, mainly in the S1 and S2 segments, with a small contribution from the S3 segment. This occurs via active transport mechanisms. There are 12 facilitative glucose transporters (GLUT-1 to GLUT-12) that transport glucose and other sugars into cells and play vital roles in glucose metabolism, including transporting glucose into and out of cells. However, the primary transporters responsible for the renal reabsorption of glucose are the 2 sodium-dependent glucose transporters SGLT1 and SGLT2. The genes coding these transporters are from 6 members of the SLC5 gene family, of which 2 have been fully characterized; 4 others exist, but their role and functions are less completely defined.

SGLT1 is a high-affinity, low-capacity glucose/galactose transporter found in the gut, brain, skeletal muscle, liver, lungs, and kidneys. It is the main sodium-dependent glucose transporter in the gastrointestinal tract, and is necessary for the normal absorption of dietary glucose. Low levels of expression are also found in the S3 segment of the proximal renal tubule, where it may contribute to the renal reabsorption of glucose; however, individuals with mutations in the SGLT1 gene exhibit severe glucose and galactose malabsorption but only mild glucosuria. SGLT1 couples absorption of 2 molecules of sodium with 1 of glucose at the intestinal brush border membrane. Transport into blood is mediated by GLUT-2, which is coupled to exchange of 3 molecules of sodium and 2 of potassium . SGLT2 is a low-affinity, high-capacity transporter that is expressed almost exclusively in the S1 and S2 segments of the renal proximal tubule, where it

is ideally placed as the main transporter responsible for renal glucose reabsorption.[33]

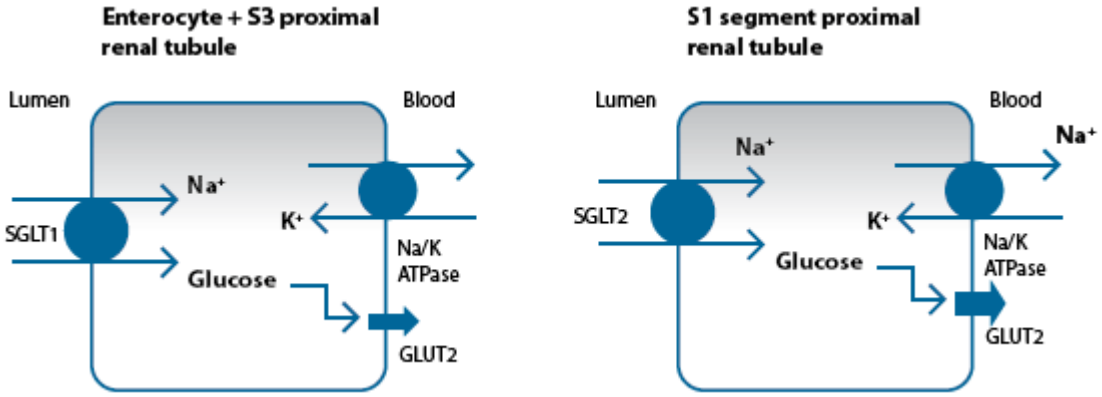


FIGURE 12: MODE OF ACTION OF SGLT1 AND SGLT2.

Both are dependent on Na/K pump to drive glucose transport. SGLT1 is a high-affinity/low-capacity glucose/galactose transporter, whereas SGLT2 a low-affinity/high-capacity glucose transporter.

In patients with uncontrolled diabetes, glucosuria is almost invariably present, and it may occur transiently even in patients with well-controlled diabetes if the renal threshold is exceeded for any significant length of time. High levels of glucosuria may lead to symptoms of polyuria and thirst, due to the osmotic effect of glucose. It has been suggested that high levels of glucosuria may also contribute to the increased risk for genitourinary fungal infections (mostly candidiasis) seen in uncontrolled diabetes, and possibly to an increased risk for urinary bacterial sepsis. Glucosuria also results in loss of energy in the urine. In patients with a blood glucose 50% above the renal threshold, this could result in the loss of 144 g of glucose -- equivalent to nearly 600 kcal energy per day in the urine. Indeed, it has been shown that a significant amount of the weight gain seen with improved glucose control with insulin therapy in type 2 diabetes is due to the abolition of

renal glucosuria; thus, paradoxically, glucosuria may be of possible benefit in patients with diabetes.[34]

Perhaps the most compelling data in support of the concept that glucosuria in the absence of diabetes is not harmful come from the study of rare individuals with the condition familial renal glucosuria. These individuals have lifelong glucosuria at varying levels as a result of mutations in the SLGT2 gene. The reported mutations occur at varying sites in the gene, and affected individuals are usually homozygotes or compound heterozygotes for such mutations, although heterozygotes may have some glucosuria. Other than glucosuria, which is usually identified by chance through medical screening or as a result of family history, most people with these genetic abnormalities appear healthy and are reported to have a normal life span. Several different mutations have been described, with varying levels of glucosuria. One individual with over 60 g/day of glucosuria was reported to show salt-wasting, with evidence of natriuresis and activation of the renin-angiotensin system, but this does not appear to be a common feature of the syndrome.

Renal glucose handling includes free glomerular filtration with complete proximal tubular reabsorption into the renal interstitial fluid space. Renal gluconeogenesis that takes place in the proximal tubular cells adds a small fraction to the glucose load that exchanges with the peri-tubular capillaries along the proximal nephron. In the distal nephron, glucose extracted can be either stored in the form of glycogen or oxidized to generate energy. In turn, no glucose is excreted in the urine and nearly all filtered glucose load perfusing the distal nephron is restored to the peripheral circulation, after mixing in the renal vein with the remainder 80% of unfiltered blood.[35]

The sodium-glucose co-transport system (SGLT) is located at the luminal membrane of the proximal renal tubular cells. These cells contain specific enzymes that enable glucose synthesis *de novo* [renal gluconeogenesis], although no enzymatic activity for concomitant glucose utilization, storage or oxidation has ever been identified in proximal tubules.

Plasma glucose is freely filtered at the glomerulus and completely reabsorbed in the proximal tubules. The SGLT-2 transporters located at the luminal membrane of cells in the S1 and S2 segments are responsible for 90% of total glucose re-uptake. The SGLT-1 transporters located downstream in the S3 segment of the proximal tubules account for the remainder 10% of the glucose load reabsorbed into the renal interstitial fluid. The process of renal gluconeogenesis occurs exclusively in the proximal tubular cells, whereas glucose utilization is limited to the distal nephron. Glycogen synthesis and storage, as well as complete glucose oxidation are detected only in cells of the distal nephron and, partial oxidation (anaerobic glycolysis) with formation and release of lactate is a characteristic of the hypoxic medullary regions of the kidney.[36]

In contrast, the distal nephron has sufficient biochemical capability to metabolize the glucose extracted from the peri-tubular fluid and, the renal medulla is in fact an obligatory site for glucose oxidation. Because most of the energy required by the mega-transport tubular activity is supplied primarily from the oxidation of fatty acids, glucose sparing by the kidney is enabled and represents a critical aspect in the maintenance of whole-body glucose homeostasis.

RENAL GLUCOSE TRANSPORT AND METABOLISM:

Various glucose transmembrane transport systems and intracellular metabolic pathways have been well characterized in the kidney. Most information is derived from *in vitro* cell preparations and renal perfusion studies Glucose is actively transported from the lumen to the tubular cells essentially by two transmembrane proteins: one with high capacity-low affinity termed sodium-glucose transport SGLT-2 and a second with high affinity-low capacity transporter termed SGLT-1. The SGLT-2 is found in the earlier S1 and S2 segments of the proximal tubule and the SGLT-1 in the S3 segment of the proximal tubules, which is also abundant in the enterocytes of the intestinal mucosa.[37]

Considering that nearly 180 liters of plasma are filtered daily by the kidneys with plasma glucose concentrations ranging between 80-120 mg/dl (an average of 100 mg/dl), the glucose load that crosses the glomeruli is estimated to be around 180 grams per day. Circulating glucose is neither protein-bound nor attached to macromolecules and thus, is freely filtered at the glomerulus. The ultrafiltrate carries the glucose towards the luminal side of the early S1 segment in the proximal tubules, where SGLT-2 is located. The active process of re-uptake of glucose is coupled with the transport of sodium cations and the complex is transferred to the cell membrane at the level of the S1 segment.[38]

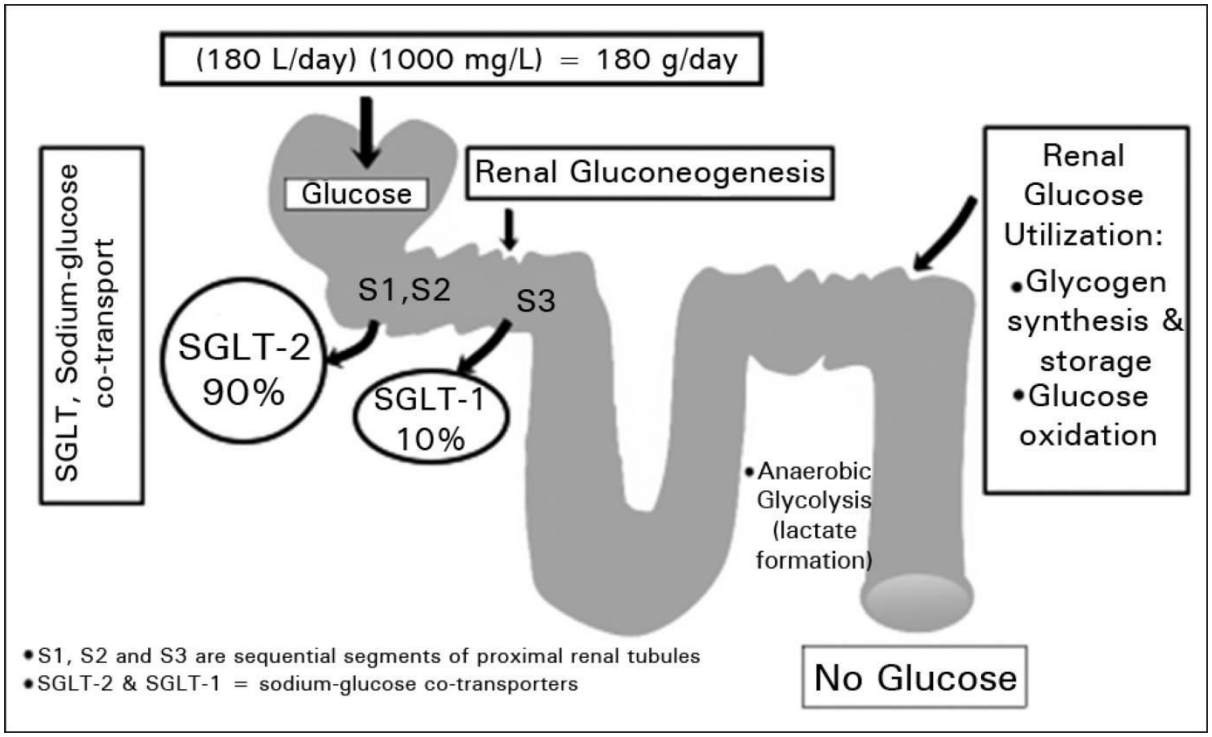


FIGURE 13:RENAL GLUCOSE UTILIZATION

This same system is also utilized to carry amino acids from the lumen into the proximal tubular cells. The SGLT-2 transport activity across the luminal membrane is driven by an electro-chemical gradient, which is created by the action of the ATPase-mediated sodium-potassium pump located in the baso-lateral membrane of the cells. The energy consumed in this active transport process is supplied entirely from ATP derived the oxidation of intracellular fatty acids.[11] As glucose builds up inside the proximal tubular cells, a facilitated passive transport in favor of a concentration gradient and mediated by GLUT-2 transporters, transfers intact glucose molecules out and into the surrounding renal interstitial fluid. In addition to restoring glucose to the interstitial fluid and eventually to the peripheral circulation, this sodium co-transport process also contributes to the maintenance of fluid and electrolyte balance by the kidney.[39]

In physiologic conditions the high capacity of the SGLT-2 co-transport system is responsible for the reabsorption of nearly 90% of all filtered glucose load. The re-uptake of the remainder 10% of the glucose load is a function of the low-capacity-high affinity SGLT-1 co-transporter and takes place downstream in the S3 segment of the proximal tubules.SGLT-1 represents a major mechanism via which glucose and galactose derived from the meals are absorbed in the intestines.

On the other hand, the fact that SGLT-2 is exclusively found in the proximal tubules of the kidney, as opposed to SGLT-1 or GLUT-2, makes this transporter suitable for more specific renal pharmacologic interventions. Thus, the possibility of interfering with the activity of the SGLT-2 has become of considerable clinical significance. It should be emphasized that there is a minor contribution to the glucose load released into the interstitial fluid provided by the process of renal gluconeogenesis.

This is possible because proximal tubular cells contain the enzymes necessary to synthesize glucose de novo, including glucose-6-phosphatase, the last step which enables newly-formed glucose to be de-phosphorylated and then secreted into the extra-cellular space. The fact that there is no detectable biochemical capacity in the proximal tubular cells to either utilize or store glucose, enables the entire filtered glucose load to be released unaffected into the renal interstitium. Thus, together with the small fraction of newly-synthesized glucose added by the proximal tubules the glucose-rich interstitial fluid exchanges with the renal venous capillaries and reaches the renal vein.[40]

Unlike the proximal nephron, cells in the distal nephron are fully capable of glucose utilization. In physiologic conditions, the amount of glucose utilized in the distal segments of the nephron equals that derived from the renal

gluconeogenesis in proximal tubules. This is confirmed by the common finding that the arterial-renal vein blood glucose concentration difference in the post-absorptive state is near zero. This is not the case however in more prolonged fasting conditions and during hypoglycemia, when a net contribution of the kidney to systemic glucose appearance has been demonstrated. The glucose extracted in the distal nephron is directed either towards glycogen synthesis for storage or to oxidative pathways, depending upon the local energy demands.

Renal glycogen accumulation is thought to provide for immediate local energy needs, when blood-borne glucose supply lags behind. The renal oxidation of glucose can be partial the release of lactate and ATP, or complete, a mitochondrial process that yields H_2O, CO_2 and ATP. Partial anaerobic glucose oxidation is more prevalent in hypoxic medullary renal conditions. Renal glucose utilization occurs exclusively in distal tubular cells and, in the absence of *glucose-6-phospatase* activity no glucose is released back into the interstitial fluid. Moreover, the small amount of glucose utilized distally does not affect the total glucose load leaving the nephron into the renal veins.

GLUCOSE HANDLING BY THE KIDNEY:

The fate of the glucose filtered, reabsorbed and excreted in the urine in normal and hyperglycemic conditions depends upon the glomerular filtration rate, the prevalent plasma concentration of glucose and the total transport capacity of the proximal tubule. There is a linear relationship between the filtered glucose load at the glomerulus and plasma glucose and thus, the glucose appearance in the ultra filtrate will be higher or lower as plasma glucose concentration increases or decreases, respectively.[41]

The proximal tubular reabsorption rate, on the other hand is only linear with the glucose load reaching the luminal membrane within a "normal" glycemic range. Once the maximum tubular reabsorption capacity of the kidney (*Tmax*,) is attained the transport process becomes saturated and glucose spills into the urine. It is worth mentioning that since the *Tmax* for glucose varies considerably among the nearly 2 millions nephrons in both kidneys, the maximum transport capacity is actually a "splay" or a range of values estimated to be around the calculated *Tmax*.

The *Tmax* can be determined by artificially elevating plasma glucose levels in a stepwise fashion up to 400-500 mg/dl with simultaneous measurements of the glomerular filtration rate, plasma and urine glucose concentrations, and urine output at given intervals. In individuals with normal kidney function, the calculated maximum tubular glucose transport has been reported between 350-450 mg/min, which corresponds to mean venous glucose concentration in the range of 180-200 mg/dl.

Hence, the normal renal threshold (*TmG*) is often referred to as the venous plasma glucose concentration ~180 mg/dl. Once this value is exceeded the SGLT system saturation transport capacity is passed and glycosuria ensues. *TmG* varies with changes in glomerular filtration rates such that during pregnancy or with a unilateral kidney, when glomerular filtration rates increase, glucosuria will occur at plasma glucose concentrations below 180 mg/dl (lower *TmG*). Conversely, when glomerular filtration decreases such as in chronic kidney disease, glucosuria is seen at plasma glucose levels higher than 220 mg/dl. Of additional interest, some apparently healthy individuals inherit a genetic abnormality characterized by a defective SGLT transport system and thus, have

constant glycosuria with normal glomerular filtration rates and in conditions of normoglycemia.[42]

The observation that the maximum tubular glucose reabsorption rate and the saturation capacity are markedly affected by chronic hyperglycaemia has provided the basis for a novel approach in the treatment of diabetes. Exposure to hyperglycemia is reportedly accompanied by an increase in tubular *TmG*, reflecting enhanced maximum glucose transport capacity and reabsorption. As a consequence, the appearance of glucose in the urine tends to occur at plasma glucose concentrations above the normal renal threshold of 180-200 mg/dl in patients with diabetes.

(*Tmax*) was expanded and the renal threshold augmented in patients with type 2 diabetes by 20-40%. More recent data derived from *in vitro* studies using cultures of proximal renal tubular cells collected from urine samples of subjects with and without diabetes fully supported these observations. In these experiments proximal tubular cells from patients with diabetes were shown to have increased mRNA expression and SGLT-2 protein content. Moreover, using a radio-labelled glucose analogue functional assay these cells also exhibited an elevated glucose transport capacity. Altogether, these results were interpreted as an indication that there is a *maladaptive* response of the kidney to hyperglycemia in diabetes mellitus. It has been speculated that by increasing glucose reabsorption rates, the kidney helps to maintain the abnormal status of hyperglycemia, which may in turn lead to further maladaptation.

INHIBITORS OF TUBULAR GLUCOSE REABSORPTION:

The possibility that the diabetic kidney perpetuates hyperglycemia gave rise to the notion that agents capable of inhibiting renal glucose reabsorption might be useful in lowering blood glucose - SGLT inhibitors would reduce the tubular capacity for glucose reabsorption and promote glucosuria at lower plasma glucose levels *(*low Tm glucose). These findings suggested that with adequate chemical blockade of the SGLT transport activity, the renal threshold for glucose reabsorption could be decreased and better glycemic control achieved in patients with diabetes.[43]

Many agents with SGLT inhibitor properties were obtained by techniques capable of chemically modifying the parent compound phlorizin ("second generation agents"). Initially in vitro experiments in cultured cell lines expressing human SGLT-1 and SGLT-2 transporters were conducted to determine the degree of selectivity of any given SGLT inhibitor using radio-ligand binding assays.

By the recent findings in humans revealing that orally ingested selective SGLT-2 inhibitors must first interact with the SGLT-1 transporters at the brush-border membrane of enterocytes. Because the enterocytes containing the SGLT-1 transporters are exposed to a greater load of the SGLT-2 specific inhibitors inside the gut, the binding affinity and thus, the selectivity is lost. As a result, the activity of the sodium-glucose/galactose co-transport process as a whole is reduced and there is a transient decline in the intestinal absorption of these sugars. The selectivity for the renal SGLT-2 transporters is nevertheless regained after partial splanchnic clearance and with lower circulating plasma drug levels.

Once selective inhibitors reach the kidney via the systemic arterial blood circulation, they bind avidly to SGLT-2 transporters in the luminal tubular membrane. In contrast, at much lower concentrations the binding affinity of these agents for the SGLT-1 transporter located downstream in the same area is severely diminished and no inhibition of the SGLT-1 activity in the kidney is detected. Following an insulin-independent decline in blood glucose, SGLT-2 inhibition is also accompanied by mild improvement in insulin sensitivity, which represents an additional mechanism by which these agents contribute to glycemic control in patients with type 2 diabetes. Moreover, recent findings reported in a SGLT-2 knockout mouse model provide evidence for an alternative approach to improving glycemic control and reducing insulin sensitivity with preservation of beta-cell function, by simply reducing the renal threshold and promoting renal glycosuria.[44]

CLINICAL PHARMACOLOGY AND PHARMACOKINETICS:

The maximum inhibitory effect achievable on the renal glucose re-uptake with the use of selective blockade of the tubular SGTL-2 transporter activity in humans has been reported at 30-50%. It has been postulated that the efficacy of these agents is somewhat limited, in part because of the competitive nature of the inhibitory binding process. There is also the possibility that very low levels of the active drug reach the tubular luminal membrane, the main site of the drug action. Finally, and perhaps most importantly, the extent to which a compensatory enhancement in the glucose reabsorption capacity of the SGLT-1 co-transporter or by a yet unidentified tubular glucose transport system, located downstream contributes to the low effectiveness of these agents has not been defined. Once plasma steady-state concentrations of the SGLT inhibitor are reached (4 to 5 days), the total amount of glucose excreted in the urine is around

50-80 grams per day. This results from the partial blockade of the SGLT-2 co-transporter and reflects a shift to the left in the maximum tubular transport capacity with a substantial decrease in the renal threshold [*TmG*].

Clinical observational studies conducted in healthy non-diabetic and in diabetic subjects have indicated that the appearance of glucosuria can be detected within 8-16 weeks after the oral intake of the first dose of an SGLT-2 inhibitor. Actually, it has been estimated that following a short therapy period with SGLT-2 inhibitors glucosuria can be detected both in subjects with and without diabetes at plasma glucose values ranging anywhere from 40-120 mg/dl. This remarkable shift in the renal threshold for glucose reabsorption contributes to a significant decrease in circulating plasma glucose, which is accomplished with a daily loss of 200-320 calories.[45]

These changes combined can provide much desired benefits for obese patients with diabetes. The decline in plasma glucose concentration following the use of SGLT inhibitors has been recently reported to be attenuated by a rise in plasma glucagon accompanied by an elevation in endogenous glucose production. These findings were documented in subjects who had received SGLT-2 inhibitors for a short period of time and who had experienced a drop in plasma glucose levels, but with no evidence of hypoglycemia. These intriguing observations have raised new questions regarding potential interactions of the kidney and liver in glucose regulation and counter-regulation.

Following oral administration SGLT-2 inhibitors are rapidly absorbed with peak plasma concentrations (median T_{max}) occurring 1-2 hours post-dose. Plasma C_{max} and the area under the curve (*AUC*) increase in a dose-proportional manner with apparent terminal half-life ($t_{1/2}$) of varying from 10 up

to 13 hours. The active drug reaches a steady-state usually within 4 to 5 days. The major metabolic elimination of SGLT-2 inhibitors is via hepatic glucuronidation and the inactive metabolites are released into peripheral circulation. There is minimal CYP3A4-mediated oxidative metabolic degradation. Thus, clinically relevant effects of other drugs on the pharmacokinetics of SGLT-2 inhibitors via cytochrome P450 are unlikely to occur. Also, since the CYP450 enzyme system is not induced and is only minimally attenuated by SGLT-2 inhibitors only negligible changes in drugs utilizing the same hepatic metabolic processes have been reported.[46]

In contrast, a decrease in total exposure to active SGLT-2 inhibitors occurs when UGT (glucuronosyl transferase) inducers, such as rifampin, phenytoin and phenobarbital are co-administered. Plasma digoxin levels tend to increase and require closer monitoring when used in combination with SGLT-2 inhibitors. When using oral radio-labeled SGLT-2 inhibitors in normal healthy volunteers nearly 50% of the active drug is recovered in feces together with minor amounts (less than 10%) of some inactive metabolites; less than 1% of the oral dose is excreted intact in the urine.

SAFETY AND EFFICACY OF SGLT INHIBITORS:

The fact that selective inhibitors of SGLT-2 lower plasma glucose concentration via an insulin-independent manner, and thus with minimal risk of hypoglycemia, combined with the potential to induce simultaneous body weight loss has generated considerable clinical interest. The mean reported decrease in the glycosylated hemoglobin (HbA_{1c}) values was approximately 1.0%, which was initially documented over a period of 6 months. More recent preliminary data have confirmed that these changes can be sustained with safety up to 4 years. The

degree of glycemic control attained with SGLT-2 inhibitors was shown to be either comparable or superior the decrease in blood glucose can be attained within a wide range of plasma glucose concentration, whether early in the disease the tubular reabsorption capacity is abnormally enhanced has not been fully determined. Moreover, with limited clinical experience and considering the added cost this class of drugs is more likely to be used later, rather than earlier in the treatment of type 2 diabetes. The possibility nevertheless of combining these agents with other well-established anti-diabetic drugs, oral and injectables seems more reasonable. Taking into account the unique mechanism of action of SGLT-2 inhibitors, maybe they are best if indicated in patients with poorly-controlled type 2 diabetes in whom oral treatment has been exhausted and the initiation of injectable agents or insulin replacement therapy is eminent.

Body weight loss was anticipated and has occurred in almost all diabetic patients who received therapy with SGLT-2 inhibitors in pivotal clinical trials. The usual amount of body weight lost was reported in the range of 2 to 4 kilograms over a period of observation of 6 months, with only a few outliers. Interestingly, studies using other drugs that promote body weight usually provide results with noticeable individual variability, whereas SGLT-2 inhibitors tend to induce nearly equal body weight loss in just about everyone treated. A recent study indicated that the majority of the weight reduction was due to the loss of body fat mass, ~50% each in the abdominal and subcutaneous fat depots, with minimal changes in lean body mass.

The stabilization of the body weight achieved 6 months after the initiation of therapy, which has been confirmed to persist up to 4 years with the continued use of SGLT-2 inhibitors is regarded as a remarkable accomplishment

and provides further reassurance to those who manage obese type 2 diabetic patients. Whether a later compensatory increase in appetite and/or a change in energy expenditure will occur in response to the loss of calories in the urine over longer periods of time. As a reminder, these agents are not approved for the sole treatment of overweight and obese individuals who do not have a diagnosis of type 2 diabetes.[47]

The low incidence of hypoglycemia is a clinically relevant and important characteristic associated with the use of SGLT-2 inhibitors in the management of type 2 diabetes. This results from the fact that the mechanisms underlying the glucose-lowering effect of a partial blockade of the tubular glucose re-uptake are insulin-independent and do not involve direct changes in insulin secretion.

Furthermore, the rate of urinary glucose excretion is proportionate to the circulating plasma glucose concentration and thus, it becomes almost negligible in conditions of very low plasma glucose concentrations. In contrast, when SGLT-2 inhibitors are used in combination with insulin secretagogues or together with insulin injections the risk for hypoglycemia is magnified.

Some important and a few unexpected findings have been reported in patients with type 2 diabetes who were exposed to various SGLT-2 inhibitors in clinical trials. Following initial treatment a transient period of polyurea, urinary frequency with increased thirst, often characterized as a simple state of dehydration was described in 3-5% of all study subjects. Two-thirds of these individuals had symptoms of postural dizziness and most of them had documented orthostatic hypotension. The majority recovered uneventfully, presumably because blood volume and fluid balance were appropriately corrected by alternate renal and some

other mechanisms. Of note, dehydration and orthostatism was more common in elderly diabetic patients who were taking anti-hypertensive drugs and/or diuretics.

Despite the transient nature of these acute hemodynamic events, greater caution and a special attention to this vulnerable population will be required by prescribing physicians and health care providers. For reasons that are not entirely clear, a slight and consistent decrease in systolic and diastolic blood pressure has been recorded in nearly all diabetic patients treated with SGLT-2 inhibitors for at least 6 months.[48]

Whether this potential beneficial effect can be related to changes in blood volume and hydration status and/or to a direct or indirect vascular dilation property of SGLT-2 inhibitors remains undetermined.

Rare cases of mild hyperkalemia following the administration of SGLT-2 inhibitors have been reported, primarily in patients with some degree of renal insufficiency. Nearly all diabetic patients who experienced serum potassium elevations were using potassium-sparing diuretics, angiotensin-converting enzyme inhibitors or angiotensin receptor blocking agents.

Considering the recommendations for the use of SGLT-2 inhibitors are limited to lower doses and should be given only to diabetic patients with estimated glomerular filtration rate (eGFR) above 30 ml/min/1.73 m^2, the occurrence of hyperkalemia is expected to be a rare event. Because of pure inefficacy, these agents are not indicated in patients with advanced end-stage renal disease and those on renal dialysis. In case of inadvertent drug overdose and intoxication, SGLT-2 inhibitors cannot be removed from the circulation efficiently by hemodialysis.

In patients with mild-to-moderate hepatic insufficiency, nonetheless there is no need for adjustments in dose, although the safety and efficacy of these SGLT-2 inhibitors have never been tested in patients with severe hepatic insufficiency. Also, the use of SGLT-2 inhibitors is contra-indicated during pregnancy and in lactating diabetic women, since newborn animals exposed to this agent exhibit a multitude of kidney and urogenital malformations.

The diagnosis was confirmed in women exposed to dapagliflozin for less than one year and in two cases the presence of breast cancer was documented within the first eight weeks of treatment. Based on these observations, the FDA concluded that there were too few events to establish causality, a decision supported by the fact that no carcinogenicity or mutagenic signal has been described during pre-clinical animal studies. Although the accumulation of large amounts of glucose in the bladder urine over time cannot be entirely rule out as a putative carcinogenic factor, it is reassuring to know that SGLT-2 transporter proteins are not expressed either in human bladder or in breast tissue.[49]

There was a noticeable increase in the incidence of urinary tract and genital infections in patients with type 2 diabetes who were treated with SGLT-2 inhibitors reported in all clinical trials. Nearly all infections were limited to the lower urinary tract and were reported in ~8-13% of participants receiving SGLT-2 inhibitors, but only in ~3-8% of those randomized to either placebo or a comparator drug. Similarly, genital infections developed in ~12-15% of patients taking SGLT-2 inhibitors, whereas those using placebo or a comparator drug had an incidence no higher than ~5%.

These observations were derived from studies that included more than 10,000 patients with type 2 diabetes followed by at least 2 years of exposure

to various SGLT-2 inhibitors. Women, especially those with a positive past medical history were more commonly affected, although the vast majority of infections resolved with standard treatment, did not require hospital admissions, and recurrences were infrequent. Actually, many of the participants who developed urinary and genital infections elected to continue with the treatment, particularly those in whom glucose control and body weight loss were apparent. Less than 2% of all patients treated with SGLT-2 inhibitors who developed genital mycosis, namely balano-postitis, were uncircumcised men.

This is an autossomal recessive disorder with either complete deficiency or decreased affinity for the SGLT-2 co-transporter protein. The genetics of "familial renal glucosuria" have been studied extensively and 21 different mutations in the gene for SGLT2 were detected. Homozygous individuals tend to have glycosuria that varies from 15 up to 200 g/day, whereas pure heterozygous family members have either mild glycosuria or none at all. Because this condition is characterized by persistent urinary glucose excretion, even within the normal range of plasma glucose concentration these individuals have difficulty maintaining body weight.[50]

There is no evidence of renal glomerular or tubular dysfunction, as assessed by kidney function and renal histological evaluations. Hypoglycemia is uncommon and the incidence of diabetes mellitus, chronic renal insufficiency and urinary tract infections is comparable to the general population. The diagnosis of "familial renal glucosuria" must be distinguished however from other complex tubular disorders that can be associated with some morbidity.

The kidney plays an important role in glucose homeostasis, contributes to glucose regulation and counter-regulation, and in sparing glucose

also helps to preserve the energy balance. These remarkable functions are achieved by an active proximal tubular mega-transport system that promotes complete glucose reabsorption and by the minimal intrinsic glucose production that often matches renal glucose utilization. Chronic hyperglycemia is associated with an increase in renal threshold and renal glucosuria occurs at higher than normal plasma glucose concentrations.

As a consequence, specific inhibition of the high capacity renal sodium-glucose co-transporter (SGLT-2) has emerged as a potential pharmacological intervention, which by decreasing tubular glucose reabsorption rates induces glucosuria and reduces blood glucose levels. In addition, continuous loss of calories in the urine is accompanied by a sustained decrease in body weight/fat in obese patients with type 2 diabetes. Initial observations in pre-clinical studies and in clinical trials have raised expectations for the utilization of SGLT-2 inhibitors in the treatment of type 2 diabetes. The data collected so far demonstrating a clinically significant glucose-lowering effect, body weight loss and negligible risk of hypoglycemia in patients treated with this novel class of drugs are very consistent.[51]

The development of transient polyuria with dehydration and the occasional hypotension, particularly in elderly diabetic patients is of concern. The high frequency of urinary tract infections and genital mycosis requires close monitoring. Lower doses of SGLT-2 can be used safely in individuals with mild-to-moderate, but not in those with severe and end-stage renal insufficiency. Whether there is any long-term damage to the kidney is unknown and cardiovascular benefits are yet to be demonstrated with the use of these novel agents. Some SGLT-2 inhibitors are now approved for the treatment of type 2

diabetes, either as monotherapy or in combination with other anti-diabetic medications. As long as patients can tolerate these agents, given all that we know today, SGLT-2 inhibitors if used with caution and in the proper patient may provide an additional safe and efficacious therapeutic option in the management of type 2 diabetes.

PLEIOTROPIC EFFECTS:

Sodium-glucose co-transporter-2 inhibitors use leads to a reduction in body weight, ranging from about 1 to 5 kg . A greater fall is seen in patients with long-standing diabetes and in those with a higher baseline weight. This weight loss is sustained after up to 2 years of use of dapagliflozin, and may be linked to a reduction in insulin dose requirements of patients with long-standing diabetes.

While it may be argued that weight loss is because of volume depletion, it has been shown that two-thirds of the decreased weight is lost from fat mass (especially visceral abnormal fat), as compared to lean mass . An initially rapid decline in weight is followed by a slower rate of weight loss, and is also marked by a reduction in weight circumference. Concomitant use of SGLT2i can attenuate or neutralize weight gain due to insulin, if given in combination with insulin.

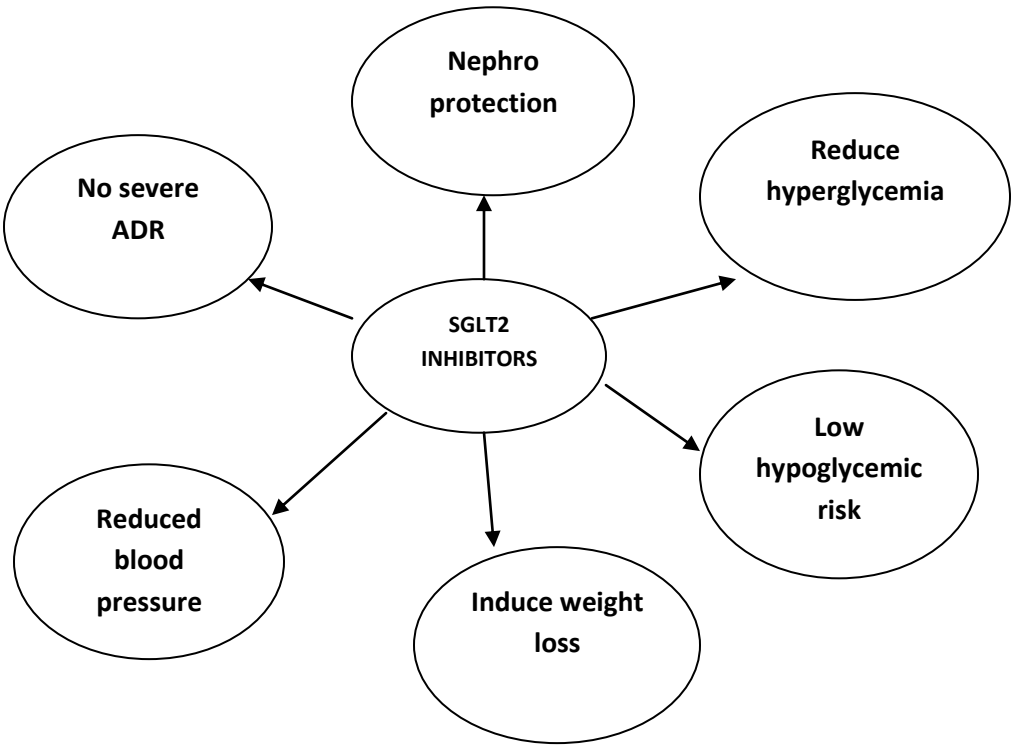


FIGURE 14: PLEIOTROPIC EFFECT OF SGLT2 INHIBITORS

Sodium-glucose co-transporter-2 inhibitors also cause significant reductions in both systolic and diastolic blood pressure (BP). These changes are relatively more prominent for systolic BP, are not dose dependent, and are not characterized by concomitant tachycardia or symptoms of hypotension/syncope in most of the cases. The effects on BP seem to be independent of glycemic or body weight reduction, and are greater in patients with high baseline systolic BP. BP reduction with SGLT2i occurs due to osmotic diuresis initially, and to local rennin-angiotensin system inhibition later on.

Uric acid levels, a marker of metabolic dysfunction, are markedly reduced (5.9–17.8%) by SGLT2i, with the effect sustained for 2 years.The drugs may affect uric acid excretion directly, by acting on its transport system, or

indirectly, but reducing sodium reabsorption in the PCT. The beneficial impact of SGLT2i on uric acid is attenuated if insulin is co-prescribed.

Renal hyperfiltration has been found to be closely associated with the development of diabetic nephropathy (DN). Pooled data from 2 randomized clinical trials including 600 patients with normo- or microalbuminuria followed up for 4 years which demonstrated that hyperfiltration has central role in pathogenesis of DN. SGLT2 is one of the main determinants of glomerular hyperfiltration and blockade of SGLT2 has potential nephroprotective action.[52]

THE FUTURE OF SGLT2 INHIBITORS:

Initial evidence that augmenting renal glucose excretion could lead to improved glycemic control has come from studies using phlorizin, a molecule originally isolated from the bark of apple tree, which inhibits both the SGLT2/1. Withdrawal of phlorizin was associated with a return to the diabetic state. Subsequently many selective SGLT2 inhibitors like Dapagliflozin, Canagliflozin, Sergliflozin, Remogliflozin, in development and ongoing trials. Dapagliflozin is approximately 1,200 times more selective for SGLT2 over SGLT1. An *in vitro* study revealed that dapagliflozin exhibited around 30 times greater potency against SGLT2 in humans than phlorizin, and approximately 4 fold less potency versus phlorizin against human SGLT1. It has demonstrated promise as mono therapy and as synergistic combination therapy with the currently available agents.[53]

It has also shown to reduce total body weight, predominantly by reducing fat mass, visceral and subcutaneous adipose tissue in inadequately controlled T2DM; and therefore improve glycemic control, stabilize insulin dosing, and reduce weight without increasing major hypoglycemic episodes. Prevention of obesity-associated hyperglycemia, improved glucose intolerance, and increased

glucose-stimulated insulin secretion support SGLT2 inhibition as a viable insulin-independent treatment and prevention of T2DM, and perhaps T1DM. However, the safety issue remains the most important parameter determining the future of any drug in development. By virtue of their nature, SGLT2 inhibitors cause glycosuria that can lead to urinary tract and genital infections, electrolyte imbalances, and increased urinary frequency. The most frequently reported adverse events in phase II and III trials include constipation, diarrhea, nausea, urinary frequency, and genitourinary infections involving UTIs and vulvovaginal infections. Although dapagliflozin appeared to be safe and well tolerated in trials until recently, it has not yet attained FDA approval, due to unanswered questions regarding safety. The U.S. Food and Drug Administration has recently approved Canagliflozin, used with diet and exercise, to improve glycemic control in adults with type 2 diabetes. Canagliflozin treatment improved glycemic control, reduced body weight and was generally well tolerated in subjects with T2DM inadequately controlled with diet and exercise. A randomized, placebo-controlled study has shown that Canagliflozin lowers postprandial glucose and insulin by delaying intestinal glucose absorption in addition to increasing urinary glucose excretion. Canagliflozin has also improved glycemic control and was generally well tolerated in subjects with T2DM and Stage 3 CKD.[54]

SGLT2 inhibitors are an exciting novel class of antidiabetic agents which are effective at reducing glycaemia, induce weight loss and reduce blood pressure with no severe adverse effects. The most frequent adverse events are an increase in urinary and genital infections, though this rarely leads to treatment discontinuation. SGLT2 inhibitors also have a very low intrinsic capacity to cause hypoglycemia. Moreover, the mechanism of action of SGLT2 inhibitors is independent of insulin secretion or action. The favorable metabolic effects of the SGLT2 inhibitors makes

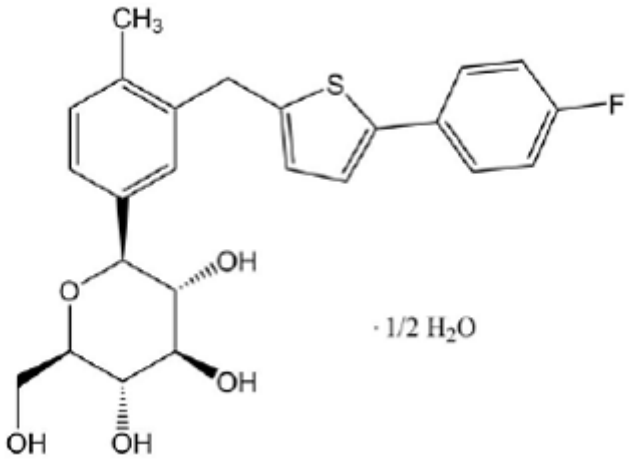
this class of oral antidiabetic agents an attractive new tool in the battle against T2DM. Nevertheless there are some issues such as cardiovascular safety and cancer risk which require close monitoring post marketing. Finally, the effect of SGLT2 inhibition in patients with impaired kidney function needs more research. There might be a protective effect on kidney function which would be an exciting new way to prevent diabetic nephropathy. However, the efficacy of the drug seems to decline as kidney function becomes more impaired. Further studies are also ongoing investigating the effect of SGLT2 inhibition in patients with type 1 diabetes, when this might also be protective for the kidney.[55]

CANAGLIFLOZIN[56]

CHEMICAL NAME: (1S)-1,5-anhydro-1-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-D-glucitol hemihydrate.

CHEMICAL FORMULA: $C_{24}H_{25}FO_5S \cdot ½\ H_2O$.

STRUCTURAL FORMULA:



CANAGLIFLOZIN

DESCRIPTION: The molecular weight is 453.53.

Inactive ingredients of the core tablet are croscarmellose sodium, hydroxypropyl cellulose, lactose anhydrous, magnesium stearate, and microcrystalline cellulose. The magnesium stearate is vegetable-creditd. The tablets are finished with a commercially available film-coating consisting of the following excipients: polyvinyl alcohol (partially hydrolyzed), titanium dioxide, macrogol/PEG, talc, and iron oxide yellow, E172 (100 mg tablet only).

DOSAGE FORM: Tablet

MECHANISM OF ACTION:

Sodium-glucose co -transporter 2 (SGLT2), expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. Canagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, canagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose (RTG), and thereby increases urinary glucose excretion (UGE).

CLINICAL PHARMACOLOGY:

PHARMACODYNAMICS:

Following single and multiple oral doses of canagliflozin in patients with type 2 diabetes, dose-dependent decreases in the renal threshold for glucose (RTG) and increases in urinary glucose excretion were observed. From a starting RTG value of approximately 240 mg/dL, canagliflozin at 100 mg and 300 mg once daily suppressed RTG throughout the 24-hour period. Maximal suppression of mean RTG over the 24-hour period was seen with the 300 mg daily dose to approximately 70 to 90 mg/dL in patients with type 2 diabetes in Phase 1 studies. The reductions in RTG led to increases in mean UGE of approximately 100 g/day in subjects with type 2 diabetes treated with either 100 mg or 300 mg of canagliflozin. In patients with type 2 diabetes given 100 mg to 300 mg once daily over a 16-day dosing period, reductions in RTG and increases in urinary glucose excretion were observed over the dosing period. In this study, plasma glucose declined in a dose-dependent fashion within the first day of dosing. In single-dose studies in healthy and type 2 diabetic subjects, treatment with canagliflozin 300 mg before a mixed-meal delayed intestinal glucose absorption and reduced postprandial glucose.

PHARMACOKINETICS:

The pharmacokinetics of canagliflozin is similar in healthy subjects and patients with type 2 diabetes. Following single-dose oral administration of 100 mg and 300 mg of CANAGLIFLOZIN, peak plasma concentrations (median Tmax) of canagliflozin occurs within 1 to 2 hours post-dose. Plasma Cmax and AUC of canagliflozin increased in a dose-proportional manner from 50 mg to 300 mg. The apparent terminal half-life (t½) was 10.6 hours and 13.1 hours for the 100 mg and 300 mg doses, respectively. Steady-state was reached after 4 to 5 days of once-daily dosing with canagliflozin 100 mg to 300 mg

ABSORPTION

The mean absolute oral bioavailability of canagliflozin is approximately 65%. Co-administration of a high-fat meal with canagliflozin had no effect on the pharmacokinetics of canagliflozin; therefore, CANAGLIFLOZIN may be taken with or without food. However, based on the potential to reduce postprandial plasma glucose excursions due to delayed intestinal glucose absorption, it is recommended that CANAGLIFLOZIN be taken before the first meal of the day.

DISTRIBUTION

The mean steady-state volume of distribution of canagliflozin following a single intravenous infusion in healthy subjects was 83.5 L, suggesting extensive tissue distribution. Canagliflozin is extensively bound to proteins in plasma (99%), mainly to albumin. Protein binding is independent of canagliflozin plasma concentrations..

METABOLISM

O-glucuronidation is the major metabolic elimination pathway for canagliflozin, which is mainly glucuronidated by UGT1A9 and UGT2B4 to two inactive O-glucuronide metabolites.

EXCRETION

Following administration of a single oral [^{14}C] canagliflozin dose to healthy subjects, 41.5%, 7.0%, and 3.2% of the administered radioactive dose was recovered in feces as canagliflozin, a hydroxylated metabolite, and an O-glucuronide metabolite, respectively. Enterohepatic circulation of canagliflozin was negligible.

Approximately 33% of the administered radioactive dose was excreted in urine, mainly as O-glucuronide metabolites (30.5%). Less than 1% of the dose was excreted as unchanged canagliflozin in urine. Renal clearance of canagliflozin 100 mg and 300 mg doses ranged from 1.30 to 1.55 mL/min.

The recommended starting dose of CANAGLIFLOZIN (canagliflozin) is 100 mg once daily, taken before the first meal of the day..

PATIENTS WITH RENAL IMPAIRMENT

The dose of CANAGLIFLOZIN is limited to 100 mg once daily in patients with moderate renal impairment with an eGFR of 45 to less than 60 mL/min/1.73 m².

CANAGLIFLOZIN should not be initiated in patients with an eGFR less than 45 mL/min/1.73 m².

Assessment of renal function is recommended prior to initiation of CANAGLIFLOZIN therapy and periodically thereafter. CANAGLIFLOZIN should be discontinued when eGFR is persistently less than 45 mL/min/1.73 m².

CONCOMITANT USE WITH UDP-GLUCURONOSYL TRANSFERASE (UGT) ENZYME INDUCERS

If an inducer of UGTs (e.g., rifampin, phenytoin, phenobarbital, ritonavir) is co-administered with CANAGLIFLOZIN, consider increasing the dosage to 300 mg once daily in patients currently tolerating CANAGLIFLOZIN 100 mg once daily who have an eGFR of 60 mL/min/1.73 m² or greater and require additional glycemic control.Consider another antihyperglycemic agent in patients with an eGFR of 45 to less than 60 mL/min/1.73 m² receiving concurrent therapy with a UGT inducer.

INDICATIONS:

- CANAGLIFLOZIN® (canagliflozin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
- **LIMITATION OF USE**
- CANAGLIFLOZIN is not recommended in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

CONTRAINDICATIONS:

- History of a serious hypersensitivity reaction to CANAGLIFLOZIN, such as anaphylaxis or angioedema.
- Severe renal impairment (eGFR less than 30 mL/min/1.73 m²), end stage renal disease (ESRD), on or patients dialysis.

WARNINGS AND PRECAUTIONS:

HYPOTENSION

CANAGLIFLOZIN causes intravascular volume contraction. Symptomatic hypotension can occur after initiating CANAGLIFLOZIN. Particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m²), elderly patients, patients on either diuretics or medications that interfere with the renin-angiotensin-aldosterone system (e.g., angiotensin converting-enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]), or patients with low systolic blood pressure..

KETOACIDOSIS

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in postmarketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including CANAGLIFLOZIN. CANAGLIFLOZIN is not indicated for the treatment of patients with type 1 diabetes mellitus.

IMPAIRMENT IN RENAL FUNCTION

CANAGLIFLOZIN increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating CANAGLIFLOZIN. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m².

HYPERKALEMIA

CANAGLIFLOZIN can lead to hyperkalemia. Patients with moderate renal impairment who are taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, or medications that interfere with the renin-angiotensin-aldosterone system are at an increased risk of developing hyperkalemia. Monitor serum potassium levels periodically after initiating CANAGLIFLOZIN in patients with impaired renal function and in patients predisposed to hyperkalemia due to medications or other medical conditions.

UROSEPSIS AND PYELONEPHRITIS

There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including CANAGLIFLOZIN.

HYPOGLYCEMIA WITH CONCOMITANT USE WITH INSULIN AND INSULIN SECRETAGOGUES

Insulin and insulin secretagogues are known to cause hypoglycemia. CANAGLIFLOZIN can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue.

GENITAL MYCOTIC INFECTIONS

CANAGLIFLOZIN increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections. Monitor and treat appropriately.

HYPERSENSITIVITY REACTIONS

Hypersensitivity reactions, including angioedema and anaphylaxis, have been reported with CANAGLIFLOZIN. These reactions generally occurred within hours to days after initiating CANAGLIFLOZIN. If hypersensitivity reactions occur, discontinue use of CANAGLIFLOZIN; treat and monitor until signs and symptoms resolve.

BONE FRACTURE

An increased risk of bone fracture, occurring as early as 12 weeks after treatment initiation, was observed in patients using CANAGLIFLOZIN.

INCREASES IN LOW-DENSITY LIPOPROTEIN (LDL-C)

Dose-related increases in LDL-C occur with CANAGLIFLOZIN. Monitor LDL-C and treat if appropriate after initiating CANAGLIFLOZIN

ADVERSE REACTION:

The following important adverse reactions are described below and elsewhere in the labeling:

- Hypotension.
- Ketoacidosis.
- Impairment in Renal Function
- Hyperkalemia
- Urosepsis and Pyelonephritis.
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues.
- Genital Mycotic Infections.
- Hypersensitivity Reactions.

- Bone Fracture.
- Increases in Low-Density Lipoprotein (LDL-C).

DRUG INTERACTIONS

UGT ENZYME INDUCERS

RIFAMPIN:

Co-administration of canagliflozin with rifampin, a nonselective inducer of several UGT enzymes, including UGT1A9, UGT2B4, decreased canagliflozin area under the curve (AUC) by 51%. This decrease in exposure to canagliflozin may decrease efficacy

DIGOXIN

There was an increase in the AUC and mean peak drug concentration (Cmax) of digoxin (20% and 36%, respectively) when co-administered with CANAGLIFLOZIN 300 mg. Patients taking CANAGLIFLOZIN with concomitant digoxin should be monitored appropriately.

POSITIVE URINE GLUCOSE TEST

Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests.

STORAGE:

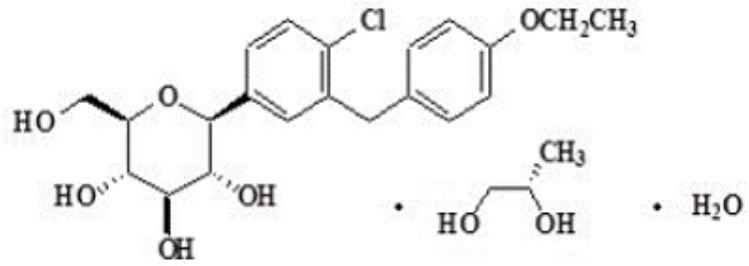
Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F).

DAPAGLIFLOZIN[57]

CHEMICAL NAME: D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, (1S)-, compounded with (2S)-1,2-propanediol, hydrate(1:1:1).

CHEMICAL FORMULA: $C_{21}H_{25}ClO_6 \cdot C_3H_8O_2 \cdot H_2O$

STRUCTURAL FORMULA:



DESCRIPTION

The molecular weight is 502.98. microcrystalline cellulose, anhydrous lactose, crospovidone, silicon dioxide, and magnesium stearate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and yellow iron oxide.

DOSAGE FORM: Tablet

MECHANISM OF ACTION:

Sodium-glucose cotransporter 2 (SGLT2), expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. Dapagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, Dapagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

GENERAL

Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in patients with type 2 diabetes mellitus following the administration of Dapagliflozin. Dapagliflozin doses of 5 or 10 mg per day in patients with type 2 diabetes mellitus for 12 weeks resulted in excretion of approximately 70 grams of glucose in the urine per day at Week 12. This urinary glucose excretion with Dapagliflozin also results in increases in urinary volume.

PHARMACOKINETICS

ABSORPTION

Following oral administration of Dapagliflozin, the maximum plasma concentration (C_{max}) is usually attained within 2 hours under fasting state. The C_{max} and AUC values increase dose proportionally with increase in Dapagliflozin dose in the therapeutic dose range. The absolute oral bioavailability of Dapagliflozin following the administration of a 10 mg dose is 78%. Administration of Dapagliflozin with a high-fat meal decreases its C_{max} by up to 50% and prolongs Tmax by approximately 1 hour.

DISTRIBUTION

Dapagliflozin is approximately 91% protein bound. Protein binding is not altered in patients with renal or hepatic impairment.

METABOLISM

The metabolism of Dapagliflozin is primarily mediated by UGT1A9; CYP-mediated metabolism is a minor clearance pathway in humans. Dapagliflozin is extensively metabolized, primarily to yield Dapagliflozin 3-O-glucuronide.

ELIMINATION

Dapagliflozin and related metabolites are primarily eliminated via the renal pathway. Following a single 50 mg dose of [14C]-Dapagliflozin, 75% and 21% total radioactivity is excreted in urine and faeces, respectively. In urine, less than 2% of the dose is excreted as parent drug. In faeces, approximately 15% of the dose is excreted as parent drug. The mean plasma terminal half-life (t½) for Dapagliflozin is approximately 12.9 hours following a single oral dose of DAPAGLIFLOZIN 10 mg.

ROUTE OF ADMINISTRATION: Oral

DOSAGE AND ADMINISTRATION:

RECOMMENDED DOSING

The recommended starting dose of DAPAGLIFLOZIN is 5 mg once daily, taken in the morning, with or without food. In patients tolerating DAPAGLIFLOZIN 5 mg once daily who require additional glycemic control, the dose can be increased to 10 mg once daily.

PATIENTS WITH RENAL IMPAIRMENT:

Initiation of DAPAGLIFLOZIN is not recommended in patients with an eGFR less than 60 mL/min/1.73 m^2.

No dose adjustment is needed in patients with mild renal impairment (eGFR of 60 mL/min/1.73 m^2 or greater).

Use of DAPAGLIFLOZIN is not recommended in patients with an eGFR persistently between 30 and less than 60 mL/min/1.73 m^2.

DAPAGLIFLOZIN is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2.

INDICATIONS:

DAPAGLIFLOZIN is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

CONTRAINDICATIONS:

- History of a serious hypersensitivity reaction to DAPAGLIFLOZIN.
- Severe renal impairment, (eGFR less than 30 mL/min/1.73 m^2) end-stage renal disease (ESRD), or patients on dialysis.

WARNINGS AND PRECAUTIONS

HYPOTENSION

DAPAGLIFLOZIN causes intravascular volume contraction. Symptomatic hypotension can occur after initiating DAPAGLIFLOZIN particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, or patients on loop diuretics. Before initiating DAPAGLIFLOZIN in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms of hypotension after initiating therapy.

KETOACIDOSIS

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in postmarketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium-glucose cotransporter 2 (SGLT2) inhibitors, including DAPAGLIFLOZIN. DAPAGLIFLOZIN is not indicated for the treatment of patients with type 1 diabetes mellitus.

Patients treated with DAPAGLIFLOZIN who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels as ketoacidosis associated with DAPAGLIFLOZIN may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, DAPAGLIFLOZIN should be discontinued, the patient should be evaluated and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid and carbohydrate replacement.

ACUTE KIDNEY INJURY AND IMPAIRMENT IN RENAL FUNCTION

DAPAGLIFLOZIN causes intravascular volume contraction cause renal impairment. Before initiating DAPAGLIFLOZIN, consider factors that may predispose patients to acute kidney injury including hypovolemia, chronic renal insufficiency, congestive heart failure, and concomitant medications .

DAPAGLIFLOZIN increases serum creatinine and decreases eGFR. Elderly patients and patients with impaired renal function may be more susceptible to these changes. Adverse reactions related to renal function can occur after initiating DAPAGLIFLOZIN. Renal function should be evaluated prior to initiation of DAPAGLIFLOZIN and monitored periodically thereafter.

Use of DAPAGLIFLOZIN is not recommended in patients with an eGFR persistently between 30 and less than 60 mL/min/1.73 m^2 and is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2.

UROSEPSIS AND PYELONEPHRITIS

There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including DAPAGLIFLOZIN. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.

HYPOGLYCEMIA WITH CONCOMITANT USE WITH INSULIN AND INSULIN SECRETAGOGUES

Insulin and insulin secretagogues are known to cause hypoglycemia. DAPAGLIFLOZIN can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when these agents are used in combination with DAPAGLIFLOZIN.

GENITAL MYCOTIC INFECTIONS

DAPAGLIFLOZIN increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections.

INCREASES IN LOW-DENSITY LIPOPROTEIN CHOLESTEROL (LDL-C)

Increases in LDL-C occur with DAPAGLIFLOZIN .

BLADDER CANCER

Bladder cancer risk factors and hematuria (a potential indicator of pre-existing tumors) were balanced between treatment arms at baseline. There are insufficient data to determine whether DAPAGLIFLOZIN has an effect on pre-existing bladder tumors. Consequently, DAPAGLIFLOZIN should not be used in patients with active bladder cancer.

ADVERSE REACTIOS:

The following important adverse reactions are described below and elsewhere in the labeling:

- Hypotension
- Ketoacidosis
- Acute Kidney Injury and Impairment in Renal Function Urosepsis and Pyelonephritis Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues
- Genital Mycotic Infections
- Increases in Low-Density Lipoprotein Cholesterol (LDL-C)
- Bladder Cancer

DRUG INTERACTIONS

POSITIVE URINE GLUCOSE TEST

Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.

DRUG INTERACTIONS

IN VITRO ASSESSMENT OF DRUG INTERACTIONS

In in vitro studies, Dapagliflozin and Dapagliflozin 3-O-glucuronide neither inhibited CYP 1A2, 2C9, 2C19, 2D6, or 3A4, nor induced CYP 1A2, 2B6, or 3A4. Dapagliflozin is a weak substrate of the P-glycoprotein (P-gp) active transporter, and Dapagliflozin 3-O-glucuronide is a substrate for the OAT3 active transporter

STORAGE:

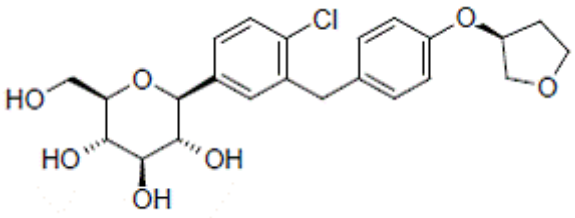
- Store DAPAGLIFLOZIN at room temperature between 68°F and 77°F (20°C and 25°C).

EMPAGLIFLOZIN[58]

CHEMICAL NAME: D-Glucitol,1,5-anhydro-1-C-[4-chloro-3-[[4-[[(3S)-tetrahydro-3furanyl]oxy]phenyl]methyl]phenyl]-, (1S).

CHEMICAL FORMULA: $C_{23}H_{27}ClO_7$

STRUCURAL FORMULA:



DESCRIPTION

Empagliflozin, an orally-active inhibitor of the sodium-glucose co-transporter 2 (SGLT2). 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.

DOSAGE FORM: Tablet

MECHANISM OF ACTION:

Sodium-glucose co-transporter 2 (SGLT2) is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Empagliflozin is an inhibitor of SGLT2. By inhibiting

SGLT2, Empagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

URINARY GLUCOSE EXCRETION

In patients with type 2 diabetes, urinary glucose excretion increased immediately following a dose of EMPAGLIFLOZIN and was maintained at the end of a 4-week treatment period averaging at approximately 64 grams per day with 10 mg Empagliflozin and 78 grams per day with 25 mg EMPAGLIFLOZIN once daily.

URINARY VOLUME

In a 5-day study, mean 24-hour urine volume increase from baseline was 341 mL on Day 1 and 135 mL on Day 5 of Empagliflozin 25 mg once daily treatment.

PHARMACOKINETICS

ABSORPTION

The pharmacokinetics of Empagliflozin has been characterized in healthy volunteers and patients with type 2 diabetes and no clinically relevant differences were noted between the two populations. After oral administration, peak plasma concentrations of Empagliflozin were reached at 1.5 hours post-dose. Thereafter, plasma concentrations declined in a biphasic manner with a rapid distribution phase and a relatively slow terminal phase. The steady state mean plasma AUC and Cmax were 1870 nmol·h/L and 259 nmol/L, respectively, with 10 mg Empagliflozin once daily treatment, and 4740

nmol·h/L and 687 nmol/L, respectively, with 25 mg Empagliflozin once daily treatment. Systemic exposure of Empagliflozin increased in a dose-proportional manner in the therapeutic dose range. The single-dose and steady-state pharmacokinetic parameters of Empagliflozin were similar, suggesting linear pharmacokinetics with respect to time.

Administration of 25 mg Empagliflozin after intake of a high-fat and high-calorie meal resulted in slightly lower exposure; AUC decreased by approximately 16% and Cmax decreased by approximately 37%, compared to fasted condition. The observed effect of food on Empagliflozin pharmacokinetics was not considered clinically relevant and Empagliflozin may be administered with or without food.

DISTRIBUTION

The apparent steady-state volume of distribution was estimated to be 73.8 L based on a population pharmacokinetic analysis. Following administration of an oral [^{14}C]-Empagliflozin solution to healthy subjects, the red blood cell partitioning was approximately 36.8% and plasma protein binding was 86.2%.

METABOLISM

No major metabolites of Empagliflozin were detected in human plasma and the most abundant metabolites were three glucuronide conjugates (2-O-, 3-O-, and 6-O-glucuronide).

ELIMINATION

The apparent terminal elimination half-life of Empagliflozin was estimated to be 12.4 h and apparent oral clearance was 10.6 L/h based on the population pharmacokinetic analysis. Following once-daily dosing, up to 22%

accumulation, with respect to plasma AUC, was observed at steady-state, which was consistent with Empagliflozin half-life. Following administration of an oral [^{14}C]-Empagliflozin solution to healthy subjects, approximately 95.6% of the drug-related radioactivity was eliminated in feces (41.2%) or urine (54.4%). The majority of drug-related radioactivity recovered in feces was unchanged parent drug and approximately half of drug-related radioactivity excreted in urine was unchanged parent drug.

OVERDOSE

- In the event of an overdose with EMPAGLIFLOZIN, contact the Poison Control Center. Employ the usual supportive measures (e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment) as dictated by the patient's clinical status.
- **ROUTE OF ADMINISTRATION:** oral

  DOSAGE AND ADMINISTRATION:

  RECOMENDED DOSAGE: The recommended dose of EMPAGLIFLOZIN is 10mg once daily in the morning, taken with or without food. In patient tolerating EMPAGLIFLOZIN, the dose may be increased to25mg.

  PATIENTS WITH RENAL IMPAIRMENT

  Assessment of renal function is recommended prior to initiation of EMPAGLIFLOZIN and periodically thereafter.

  EMPAGLIFLOZIN should not be initiated in patients with an eGFR less than 45 mL/min/1.73 m².No dose adjustment is needed in patients with an eGFR greater than or equal to 45 mL/min/1.73 m².

EMPAGLIFLOZIN should be discontinued if eGFR is persistently less than 45 mL/min/1.73 m²

INDICATIONS

EMPAGLIFLOZIN is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

EMPAGLIFLOZIN is not recommended for patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

CONTRA INDICATIONS

- History of serious hypersensitivity reaction to EMPAGLIFLOZIN.
- Severe renal impairment, end stage renal disease or dialysis

WARNINGS AND PRECAUTIONS

HYPOTENSION

EMPAGLIFLOZIN causes intravascular volume contraction. Symptomatic hypotension may occur after initiating EMPAGLIFLOZIN. Particularly in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics.

Patients treated with EMPAGLIFLOZIN who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels, as ketoacidosis associated with EMPAGLIFLOZIN may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, EMPAGLIFLOZIN should be discontinued, patient should be evaluated, and prompt treatment

should be instituted. Treatment of ketoacidosis may require insulin, fluid and carbohydrate replacement.

In many of the postmarketing reports, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized and institution of treatment was delayed because presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath .

IMPAIRMENT IN RENAL FUNCTION

EMPAGLIFLOZIN increases serum creatinine and decreases eGFR.The risk of impaired renal function with EMPAGLIFLOZIN is increased in elderly patients and patients with moderate renal impairment. More frequent monitoring of renal function is recommended in these patients . Renal function should be evaluated prior to initiating EMPAGLIFLOZIN and periodically thereafter.

UROSEPSIS AND PYELONEPHRITIS

There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including EMPAGLIFLOZIN. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections.

HYPOGLYCEMIA WITH CONCOMITANT USE WITH INSULIN AND INSULIN SECRETAGOGUES

Insulin and insulin secretagogues are known to cause hypoglycemia. The risk of hypoglycemia is increased when EMPAGLIFLOZIN is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin.

GENITAL MYCOTIC INFECTIONS

EMPAGLIFLOZIN increases the risk for genital mycotic infections. Patients with a history of chronic or recurrent genital mycotic infections were more likely to develop mycotic genital infections.

INCREASED LOW-DENSITY LIPOPROTEIN CHOLESTEROL

Increases in LDL-C can occur with EMPAGLIFLOZIN. Monitor and treat as appropriate.

MACROVASCULAR OUTCOMES

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with EMPAGLIFLOZIN or any other antidiabetic drug.

ADVERSE REACTION:

The following important adverse reactions are described below and elsewhere in the labeling:

- Hypotension
- Ketoacidosis Impairment in Renal Function
- Urosepsis and Pyelonephritis

- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues
- Genital Mycotic Infections
- Increased Low-Density Lipoprotein Cholesterol (LDL-C)

DRUG INTERACTIONS

DIURETICS

Co administration of Empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion.

INSULIN OR INSULIN SECRETAGOGUES

Co administration of Empagliflozin with insulin or insulin secretagogues increases the risk for hypoglycemia.

POSITIVE URINE GLUCOSE TEST

Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests.

STORAGE

- Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F)

REVIEW OF LIERATURE

1. **Cersosimo E[59] et al.,** The importance of the kidney in glucose homeostasis has been recognized for many years. Recent observations indicating a greater role of renal glucose metabolism in various physiologic and pathologic conditions have rekindled the interest in renal glucose handling as a potential target for the treatment of diabetes. The enormous capacity of the proximal tubular cells to reabsorb the filtered glucose load entirely, utilizing the sodium-glucose co-transporter systembecame the focus of attention. Subsequently, several compounds with more selective SGLT-2 inhibition properties were developed. . In general, a 6-month period of therapy with SGLT-2 inhibitors is followed by a mean urinary glucose excretion rate of ~80 g/day accompanied by a decline in fasting and postprandial glucose with average decreases in HgA1C ~1.0%. Concomitant body weight loss and a mild but consistent drop in blood pressure also have been reported. In contrast, transient polyuria, thirst with dehydration and occasional hypotension have been described early in the treatment. In addition, a significant increase in the occurrence of uro-genital infections, particularly in women has been documented with the use of SGLT-2 inhibitors.

2. **Singh AK[60] et al.,**The gradual decline in β-cell function is inevitable in type 2 diabetes mellitus and therefore, substantial proportions of patients require insulin subsequently, in order to achieve optimal glucose control. While weight gain, hypoglycemia, and fluid retention especially during dose intensification is a known limitation to insulin therapy, these adverse effects also reduce patient satisfaction and treatment adherence. It is also possible that the benefits of intensive control achieved by insulin therapy, perhaps get nullified by the weight gain and hypoglycemia. In addition, improvement in plasma glucose or glycated hemoglobin (HbA1c) itself is associated with weight gain. Notably, studies have already suggested that reduction in body weight by ~3-5%, may allow a significantly better glycemic control. Thus, a class of drugs, which can reduce HbA1c effectively, yet are weight neutral or preferably reduce body weight, could be the most sought out strategy as an add-on therapy to insulin. While sulfonylureas (SUs) are associated with weight gain and hypoglycemia, pioglitazone increases body weight and fluid retention. Moreover, SUs are not recommended once premix or prandial insulin is commenced. The addition of newer agents, such as glucagon-like peptide-1 receptor agonist to insulin

certainly appears to be an effective tool in reducing both HbA1c and body weight as is evident across the studies; however, this approach incurs an additional injection as well as cost. Dipeptidyl peptidase-4 inhibitors (DPP-4I) and sodium-glucose co-transporter-2 inhibitors (SGLT-2I) are other exciting options, as an add-on to insulin therapy primarily these drugs and do not possess any intrinsic potential of hypoglycemia. Furthermore, these are either weight neutral or induce significant weight loss.

3. **James F List[61] et al.,**Dapagliflozin, a novel inhibitor of renal sodium-glucose cotransporter 2, allows an insulin-independent approach to improve type 2 diabetes hyperglycemia.Type 2 diabetic patients were randomly assigned to one of five dapagliflozin doses, metformin XR, or placebo for 12 weeks. The primary objective was to compare mean change from baseline in A1C. Other objectives included comparison of changes in fasting plasma glucose (FPG), weight, adverse events, and laboratory measurements. After 12 weeks, dapagliflozin induced moderate glucosuria (52-85 g urinary glucose/day) and demonstrated significant glycemic improvements versus placebo (DeltaA1C -0.55 to -0.90% and DeltaFPG -16 to -31 mg/dl). Weight loss change versus placebo was -1.3 to -2.0 kg. There was no change in renal function. Serum uric acid decreased, serum magnesium increased, serum phosphate increased at higher doses, and dose-related 24-h urine volume and hematocrit increased, Treatment-emergent adverse events were similar across all groups. Dapagliflozin improved hyperglycemia and facilitates weight loss in type 2 diabetic patients by inducing controlled glucosuria with urinary loss of approximately 200-300 kcal/day. Dapagliflozin treatment demonstrated no persistent, clinically significant osmolarity, volume, or renal status changes.

4. **Mudaliar S[62] et al.,** Type 2 diabetes is a chronic disease with disabling micro- and macrovascular complications that lead to excessive morbidity and premature mortality. Although insulin resistance and insulin secretory defects play a major role in the pathogenesis of hyperglycemia, metabolic defects contribute to the initiation/worsening of the diabetic state. Instead of an increase in renal glucose excretion, which could ameliorate hyperglycemia, there is an increase in renal glucose reabsorption, which helps sustain hyperglycemia in patients with diabetes. The sodium-glucose cotransporter (SGLT) 2 inhibitors are novel antidiabetes agents that inhibit renal glucose reabsorption and promote glucosuria, thereby leading to reductions in plasma glucose concentrations.

5.**Riggs K[63] et al.,**The concurrent management of type 2 diabetes mellitus (T2DM) and chronic congestive heart failure presents several therapeutic challenges. insulin and insulin-sensitizing medications detrimentally "flood" the heart with energy-providing substrates, including fats and glucose. Sodium glucose cotransporter-2 (SGLT-2) inhibitors, a new class of antidiabetic medication, operate via this principle by blocking the reabsorption of glucose in the kidney and subsequently releasing glucose through the urine. the potential role of SGLT-2 inhibitor therapy in patients with concurrent T2DM and chronic heart failure. SGLT-2 inhibitors are safe and can be recommended to treat T2DM in patients with chronic heart failure and intact renal function. Further studies are in progress to assess long-term survival benefits.

6. **Halimi S[64] et al.,** In type 2 diabetes (T2DM), glycaemic control delays the development and slows the progression of complications. Although there are numerous glucose-lowering agents in clinical use, only approximately half of T2DM patients achieve glycaemic control. Sodium-glucose cotransporter-2 inhibitors (SGLT-2-i) have recently been developed for the treatment of T2DM. The available data suggest a good tolerability profile for the three available drugs - canagliflozin, dapagliflozin and empagliflozin - approved by the US Food and Drug Administration (FDA) for the American market as well as in other countries. The most frequently reported adverse events with SGLT-2 are female genital mycotic infections, urinary tract infections and increased urination. The pharmacodynamic response to SGLT-2-i declines with increasing severity of renal impairment, requiring dosage adjustments or restrictions with moderate-to-severe renal dysfunction. Most patients treated with SGLT-2 also have a modest reduction in blood pressure and modest effects on serum lipid profiles, some of which are beneficial .In patients treated with dapagliflozin, a non-significant excess number of breast and bladder cancers has been reported; Although there is some benefit for several cardiovascular risk factors such as HbA1c, high blood pressure, obesity and increases in LDL-C, adequately powered trials are still required to determine the effects of SGLT-2 on macrovascular outcomes.

7. **Storgaard H[65] et al.,** Sodium-glucose co-transporter 2 inhibitors (SGLT-2) increase urinary glucose excretion through a reduced renal glucose reabsorption. meta-analyses of randomised clinical trials on SGLT-2 versus placebo, other oral glucose lowering drugs or insulin for patients with type 2 diabetes will be performed. The primary end point will be the glycated haemoglobin. Secondary

end points will include changes in body weight, body mass index, fasting plasma glucose, plasma cholesterol, kidney and liver blood tests, blood pressure and adverse events. Electronic and manual searches will be performed. Meta-analyses will be performed and the results presented as mean differences for continuous outcomes and risk differences for dichotomous outcomes, both with 95% CIs. Subgroup, sensitivity, regression and sequential analyses will be performed to evaluate inter trial heterogeneity, bias and the robustness of results due to cumulative testing.

8. **Schnell O[66] et al.,**The role for the novel treatment approach of sodium-glucose cotransporter-2 (SGLT-2) in type 2 diabetes is increasing. Structured self-monitoring of blood glucose (SMBG), based on a less intensive and a more intensive scheme, may contribute to an optimization of SGLT-2 inhibitor based treatment. The expert recommendation suggests individualized approaches of SMBG, using simple and clinically applicable schemes. Potential benefits of SMBG in SGLT-2 inhibitor based treatment approaches are early assessment of treatment success or failure, timely modification of treatment, detection of hypoglycemic episodes, assessment of glucose excursions, and support of diabetes management and education. The length and frequency of SMBG should depend on the clinical setting and the quality of metabolic control

9.**Tahrani AA[67] et al.,**The two main sodium-glucose cotransporters (SGLTs), SGLT1 and SGLT2, provide new therapeutic targets to reduce hyperglycaemia in patients with diabetes. SGLT1 enables the small intestine to absorb glucose and contributes to the reabsorption of glucose filtered by the kidney. SGLT2 is responsible for reabsorption of most of the glucose filtered by the kidney. Inhibitors with varying specificities for these transporters (eg, dapagliflozin, canagliflozin, and empagliflozin) can slow the rate of intestinal glucose absorption and increase the renal elimination of glucose into the urine. Results of randomised clinical trials have shown the blood glucose-lowering efficacy of SGLT inhibitors in type 2 diabetes when administered as monotherapy or in addition to other glucose-lowering therapies including insulin. Increased renal glucose elimination also assists weight loss and could help to reduce blood pressure. Effective SGLT2 inhibition needs adequate glomerular filtration and might increase risk of urinary tract and genital infection, and excessive inhibition of SGLT1 can cause gastro-intestinal symptoms. However, the insulin-independent mechanism of action of SGLT inhibitors seems to offer durable glucose-lowering efficacy with low risk of clinically significant

hypoglycaemia at any stage in the natural history of type 2 diabetes. SGLT inhibition might also be considered in conjunction with insulin therapy in type 1 diabetes.

10.**Singh AK[68] et al.,** As type 2 diabetes mellitus (T2DM) is a chronic and progressive disease with multiple pathophysiologic defects, no single anti-diabetic agent can tackle all these multi-factorial pathways. Consequently, multiple agents working through the different mechanisms will be required for the optimal glycemic control. Moreover, the combination therapies of different anti-diabetic agents may complement their actions and possibly act synergistic. Sodium-glucose co-transporter-2 inhibitors (SGLT-2I) are newly emerging class of drugs, with a great potential to reduce glucose effectively with an additional quality of lowering cardiovascular events However, increase in endogenous glucose production (EGP) from the liver, either due to the increase in glucagon or compensatory response to glucosuria can offset the glucose-lowering potential of SGLT-2I. Interestingly, another class of drugs such as dipeptidyl peptidase-4 inhibitors (DPP-4I) effectively decrease glucagon and reduce EGP. In light of these findings, combination therapies with SGLT-2I and DPP-4I are particularly appealing and are expected to produce a synergistic effect. Preclinical studies of combination therapies with DPP-4I and SGLT-2I have already demonstrated a significant lowering of hemoglobin A1c potential and human studies also find no drug-drug interaction between these agents.

11.**Rosenwasser RF[69] et al.,** sodium glucose co-transporter 2 (SGLT-2) inhibitors lower glucose by enhancing its excretion by blocking reabsorption in the renal tubules, thus eliminating glucose from the body along with the molecules' attendant effects on caloric balance, plasma osmolality, and lipids. Consequently, SGLT-2 inhibitors improve glucose control to an extent comparable to other hypoglycemic agents while simultaneously reducing body weight, blood pressure, and cholesterol . One agent, canagliflozin, has recently been approved by the US Food and Drug Administration (FDA) and two other agents have progressed through Phase III trials, including dapagliflozin and empagliflozin. Collectively, when used as monotherapy, these agents have demonstrated reductions in hemoglobin A1c (HbA1c), body weight, and blood pressure of -0.34% to -1.03%, -2.0 to -3.4 kg, and -1.7 to -6.4 mmHg/-0.3 to -2.6 mmHg (systolic blood pressure/diastolic blood pressure), respectively. SGLT-2 inhibitors have been well tolerated, with hypoglycemia (0.9% to 4.3%) occurring infrequently in clinical trials. Safety signals related to breast and bladder cancer have arisen with dapagliflozin. As these agents emerge, clinicians should embrace the addition to the formulary for treating type 2 diabetes, but must also weight the risk-benefit of this new class in deciding which patient types are most likely to benefit from their novel mechanism of action.

12. **Albarrán OG[70] et al.,**Dapagliflozin is the first novel sodium-glucose co-transporter-2 (SGLT2) inhibitor approved by the European Medicines Agency (EMA) for the treatment of type 2 diabetes. By inhibiting SGLT2, dapagliflozin blocks reabsorption of filtered glucose in the kidney, increasing urinary glucose excretion and reducing blood glucose levels. Its mechanism of action is independent of pancreatic β cell function and modulation of insulin sensitivity. The results of phase III clinical trials showed that dapagliflozin, at a dose of 5 or 10mg/day for 24 weeks as monotherapy in previously untreated patients, or as add-on combination therapy with metformin, glimepiride, pioglitazone or insulin-based therapy, significantly reduced both HbA1c and fasting plasma glucose levels compared with placebo. In addition, dapagliflozin was noninferior to glipizide, in terms of glycemic control after 52 weeks, when used as add-on therapy in patients with type 2 diabetes inadequately controlled with metformin. In most clinical trials, dapagliflozin reduced body weight. The combination of both effects (improved glycemic control and weight loss) is achieved to a greater extent in treatments that include dapaglifozin. Longer-term extension studies indicated that the efficacy of dapagliflozin on the glycemic control and weight reductión is maintained for up to 2 and 4 years. Dapagliflozin was well tolerated. Genital infections and urinary tract infections were more frequent in patients who received dapagliflozin than in placebo recipients. Hypoglycemic episodes were scarce with dapagliflozin. In conclusion, dapagliflozin is a novel option for the management of type 2 diabetes, particularly when used as add-on therapy.

13.**Zhang Q[71] et al.,**In search of add-on treatments to metformin, sodium-glucose cotransporter-2 (SGLT-2) inhibitors are potential candidates. This meta-analysis examines the potential use of SGLT-2 inhibitors in combination with metformin as a therapeutic option for type 2 diabetes management in patients with inadequate control with metformin.A literature search was made in several databases for randomized controlled trials (RCTs) utilizing metformin therapy combined with SGLT-2 inhibitors or placebo. Heterogeneity was estimated with I(2) statistics and random effect model was chosen for the meta-analyses of mean differences in changes from baseline in both SGLT-2 inhibitor treated and control groups Seven RCTs were selected for the meta-analysis. In comparison with placebo-MET, the SGLT-2 inhibitor-MET combination therapy resulted in significant HbA1c decline in 12-24 week duration, to less

extent after 1 year (-0.37 [-0.77, 0.03]; P=0.07) but not by 2 year (-0.41 [-1.09, 0.28]; P=0.24) duration. SGLT-2 inhibitor-MET significantly lowered FPG and body weight after 24 weeks, 1 year, and 2 years. Systolic and diastolic blood pressure declined only in the short-term (12-24 weeks). After 2 years, neither systolic (-1.80 [-6.18, 2.58]; P=0.42) nor diastolic blood pressure (-0.20 [-2.94, 2.54]; P=0.89) declined significantly more than control. Incidence of suspected genital infections was slightly more in SGLT-2 inhibitor-MET group.

14.**Gilbert RE[72] et al.,** With the advent of sodium-glucose linked transporter-2 (SGLT-2) inhibitors, physicians are now aware that the kidney also needs to be considered in the spectrum of action of anti-hyperglycaemic agents. Though familiar with the need for dose adjustment when prescribing many of our current anti-hyperglycaemic drugs in the setting of kidney dysfunction, with the SGLT-2 inhibitors pharmacodynamic as well as pharmacokinetic aspects also need to be considered. Finally, through their ability to reduce intraglomerular pressure, systemic blood pressure and plasma uric acid concentration, the SGLT-2 inhibitors offers the possibility of kidney protection. An hypothesis that will need to be tested with long term studies that address changes in the kidney beyond albuminuria, assessing the rate of decline in glomerular filtration rate and 'hard' kidney related endpoints such as the need for renal replacement therapy (dialysis, transplantation) will be important in this setting.

15.**Gallo LA[73] et al.,** Traditional treatments for type 1 and type 2 diabetes are often associated with side effects, including weight gain and hypoglycaemia that may offset the benefits of blood glucose lowering. The kidneys filter and reabsorb large amounts of glucose, and urine is almost free of glucose in normo glycemia. The sodium-dependent glucose transporter (SGLT)-2 in the early proximal tubule reabsorbs the majority of filtered glucose. Remaining glucose is reabsorbed by SGLT1 in the late proximal tubule. Diabetes enhances renal glucose reabsorption by increasing the tubular glucose load and the expression of SGLT2, which maintains hyperglycaemia. Inhibitors of SGLT2 enhance urinary glucose excretion and thereby lower blood glucose levels in type 1 and type 2 diabetes. The load-dependent increase in SGLT1-mediated glucose reabsorption explains why SGLT2 inhibitors in normoglycaemic conditions enhance urinary glucose excretion to only ~50% of the filtered glucose. The role of SGLT1 in both renal and intestinal glucose reabsorption provides a rationale for the development of dual SGLT1/2 inhibitors. SGLT2 inhibitors lower blood glucose levels independent of insulin and induce pleiotropic actions that may be

relevant in the context of lowering cardiovascular risk. Ongoing long-term clinical studies will determine whether SGLT2 inhibitors have a safety profile and exert cardiovascular benefits that are superior to traditional agents.

16.**Zanoli L[74] et al.,**SGLT2 inhibitors are new antihyperglycaemic agents whose ability to lower glucose is directly proportional to GFR. Therefore, in chronic kidney disease (CKD) the blood glucose lowering effect is reduced. Unlike many current therapies, the mechanism of action of SGLT2 inhibitors is independent of insulin action or beta-cell function. In addition, the mechanism of action of SGLT2 inhibitors is complementary and not alternative to other antidiabetic agents. SGLT2 inhibitors could be potentially effective in attenuating renal hyperfiltration and, consequently, the progression of CKD. Moreover, the reductions in intraglomerular pressure, systemic blood pressure, and uric acid levels induced by SGLT inhibition may potentially be of benefit in CKD subjects without diabetes. However, at present, only few clinical studies were designed to evaluate the effects of SGLT2 inhibitors in CKD. Consequently, safety and potential efficacy beyond blood glucose lowering should be better clarified in CKD.

17.**Marques AR[75] et al.,**Who never had a type 2 obese diabetic patient, treated by several oral antidiabetic drugs and insulin, with consequent weight gain associated with the therapeutic escalation and uncontrolled diabetes The arrival of GLP-1 agonists and SGLT-2 inhibitors allows to reevaluate the management of these patients, with their favorable effects on glycemic control, weight and the risk of hypoglycemia and their complementary mechanisms to conventional treatments. The vicious cycle of weight gain and increased need of insulin is limited. The choice between these two molecules must be based on several factors (glycemic target, weight, comorbidities, route of administration, side effects, etc.), and the balanced enthusiasm of these new treatments with the insufficient data regarding their long-term safety and their impact on micro- and macrovascular complications

18. **Goring S[76] et al.,** Indirect evidence from randomized controlled trials (RCTs) was used to estimate the effect of dapagliflozin, a new agent with a novel mechanism of action (SGLT-2 inhibition), relative to other anti-diabetes therapies after 1 year of treatment. RCTs enrolling subjects with type 2 diabetes inadequately controlled on metformin monotherapy were included. Comparators included dipeptidyl peptidase-4 (DPP-4) inhibitors, thiazolidinediones (TZDs), sulphonylureas, glucagon-like peptide-1 (GLP-1) analogues and dapagliflozin.

Outcomes of interest were mean change from baseline HbA1c, weight and systolic blood pressure, and incidence of hypoglycaemia. From 4270 abstracts, six RCTs were included in the primary analysis; no RCTs involving GLP-1 analogues met primary inclusion criteria. All RCTs were actively controlled with sulphonylureas. The mean change in HbA1c from baseline was similar across comparators. The treatment effect (95% credible interval) of dapagliflozin on HbA1c was -0.08% (-0.25, 0.10) relative to DPP-4 inhibitors, -0.02% (-0.24, 0.21) relative to TZDs and 0.00% (-0.16, 0.16) relative to sulphonylureas. Non-sulphonylureas showed significantly lower risk of hypoglycaemia relative to sulphonylureas. Dapagliflozin had a significant effect on weight change: the relative difference was -2.74 kg (-5.35, -0.10) compared with DPP-4 inhibitors, and -4.67 kg (-7.03, -2.35) compared with sulphonylureas.

19. **Kleefstra N[77] et al.,** To describe the efficacy and safety of dapagliflozin, the first sodium-glucose co-transporter-2 (SGLT-2) inhibitor for the treatment of diabetes mellitus type 2 (DM2) to be registered in the Netherlands. We searched the Medline database for articles on the use of dapagliflozin in patients with DM2. We included randomised studies with a minimum duration of 12 weeks and systematic reviews published up to 19 October 2012. Two assessors selected the articles on the basis of title, abstract and if necessary, the complete text.Eleven articles were suitable for analysis. On comparison with placebo, the use of dapagliflozin gave a drop in HbA1c-value of approximately 0.5-0.8 percentage points (6-9 mmol/mol). The body weight of patients who used dapagliflozin dropped between 1.0-2.4 kg on comparison with the placebo and metformin control groups. Urinary tract infections occurred twice as often and genital infections three to four times more often. There were no data on the effect on micro- and macrovascular complications or on mortality.

20.**Rudofsky G[78] et al.,**Since end of 2012 a new therapeutical approach for the treatment of type 2 diabetes is available in Germany. It relies on the modulation of glucose re-absorption in the kidney by inhibition of so called Sodium Glucose Linked Transporters (SGLT) thereby leading to therapeutical glucosuria. Putting the kidney in the centre of therapeutical approach of glucose regulation is unfamiliar for physicians. Therefore, it is helpful to elucidate the underlying renal mechanisms and to present the advantages and disadvantages of this new therapeutic class.

21.**Bhartia M[79] et al.,**The prevalence of type 2 diabetes is increasing worldwide. The majority of currently available glucose-lowering agents work via insulin-dependent mechanisms and have significant limitations. Hence, there is a need for newer treatments utilizing novel therapeutic targets. Drugs which inhibit the sodium glucose cotransporter in the renal tubules (SGLT-2 inhibitors), represent a novel class of drugs under development. By inhibiting SGLT-2, they promote increased renal glucose excretion and thereby calorie loss with improved glycemic control and weight loss. Dapagliflozin is most advanced in development of this new drug class and currently undergoing phase 3 trials. In addition to its glucose lowering effect, dapagliflozin appears to have favorable impacts on weight and blood pressure, with low risk of hypoglycemia. However, as with all new treatments, long-term safety is an issue. Clinical trials showed increased risk of genital and possibly urinary infections with dapgliflozin. Furthermore, concerns have arisen regarding a possible increased incidence of breast and bladder cancer in patients on dapagliflozin.

22.**Abdul-Ghani MA[80] et al.,**Hyperglycemia plays an important role in the pathogenesis of type 2 diabetes mellitus, i.e., glucotoxicity, and it also is the major risk factor for microvascular complications. Thus, effective glycemic control will not only reduce the incidence of microvascular complications but also correct some of the metabolic abnormalities that contribute to the progression of the disease. Achieving durable tight glycemic control is challenging because of progressive β-cell failure and is hampered by increased frequency of side effects, e.g., hypoglycemia and weight gain. Most recently, inhibitors of the renal sodium-glucose cotransporter have been developed to produce glucosuria and reduce the plasma glucose concentration. These oral antidiabetic agents have the potential to improve glycemic control while avoiding hypoglycemia, to correct the glucotoxicity, and to promote weight loss. In this review, we will summarize the available data concerning the mechanism of action, efficacy, and safety of this novel antidiabetic therapeutic approach.

23.**Kinne RK[81] et al.,**Recently, the idea has been developed to lower blood glucose blood glucose levels in diabetes by inhibiting sugar reabsorption sugar reabsorption in the kidney . The main target is thereby the early proximal tubule secondary active transport of the sugar is mediated by the sodium-D: -glucose D-glucose cotransporter SGLT2 SGLT2 . A model substance for the inhibitors inhibitors is the O-glucoside O-glucoside phlorizin phlorizin which inhibits

transport transport competitively. Its binding to the transporter involves at least two different domains: aglycone binding site at the transporter surface, involving extramembranous loops sugar binding /translocation site buried in a hydrophilic pocket of the transporter. The properties of these binding sites differ between SGLT2 and SGLT1 SGLT1 , which mediates sugar absorption in the intestine Various O-, C-, N- and S-glucosides have been synthesized with high affinity and high specificity for SGLT2 . Some of these glycosides are in clinical trials and have been proven to successfully increase urinary glucose excretion and to decrease blood sugar levels without the danger of hypoglycaemia during fasting in type 2 diabetes .

24. **Washburn WN[82] et al.,**A critical factor for maintenance of glucose balance is the renal recovery of glucose from the glomerular filtrate mediated primarily by sodium glucose co-transporter 2 (SGLT2). This capacity can be modulated by SGLT2 inhibitors thereby providing a unique insulin independent method of treatment of diabetes.These compounds comprise O, C and N-glycosides generated by attachment of an appropriate lipophilic aglycone component to a suitable glucose analogue.The realization that the in vivo potency of O-glucosides was markedly less than that of C-glucosides necessitated a shift in medicinal chemistry focus of the pharmaceutical companies pursuing SGLT2 inhibitors. The role of SGLT2 inhibitors for treatment of diabetes will be established by the outcome of the five compounds in advanced clinical trials.

25.**Wan HX[83] et al.,**Sodium-glucose co-transporters are a family of glucose transporter found in the intestinal mucosa of the small intestine (SGLT-2) and the proximal tubule of the nephron (SGLT-1 and SGLT-2). They contribute to renal glucose reabsorption and most of renal glucose (about 90%) is reabsorbed by SGLT-2 located in the proximal renal tubule. Selectively inhibiting activity of SGLT-2 is an innovative therapeutic strategy for treatment of type 2 diabetes by enhancing urinary glucose excretion from the body. Therefore SGLT-2 inhibitors are considered to be potential antidiabetic drugs with an unique mechanism. This review will highlight some recent advances and structure-activity relationships in the discovery and development of SGLT-2 inhibitors including O-glycoside, C-glycoside, C, O-spiro glycoside and non glycosides.

26. **Imprialos KP[84] et al.,**Diabetes mellitus is a major issue of public health, affecting more than 300 million people worldwide. Inhibitors of the sodium-glucose cotransporter-2 (SGLT-2) in the renal proximal tubule are a novel class of agents for the treatment of type 2 diabetes mellitus. Inhibition of the SGLT-2

results in reduced glucose reabsorption and improvement in glycemic control. Alongside glucose excretion, SGLT-2 inhibitors also have mild natriuretic and diuretic effects, combining actions of a proximal tubule diuretic and an osmotic diuretic; these properties are expected to lead to small blood pressure (BP) reductions. Clinical studies with dapagliflozin, canagliflozin, empagliflozin, ipragliflozin, luseogliflozin, and tofogliflozin used either as monotherapy or add-on therapy and compared with placebo or active treatment have also examined the effect of these agents on BP as a secondary endpoint. Although with some differences between individual agents, all of the approved SGLT-2 inhibitors provided a mild but meaningful reduction in SBP and DBP. Recent studies with the use of ambulatory blood pressure monitoring suggest that the magnitude of this BP reduction can be even greater.

27.**Lucio R. Volino[85] et al.,**Diabetes mellitus continues to be a major health issue worldwide. Despite all of the treatment options available on the market, many patients with diabetes fail to reach their treatment goals. Novel agents such as the Sodium-Glucose Cotransporter 2 (SGLT2) inhibitors show promise in effectively lowering blood glucose. Objective: To review the scientific literature for efficacy information regarding the use of approved SGLT2 inhibitors (canagliflozin, dapagliflozin and empagliflozin) in the treatment of Type 2 Diabetes Mellitus (T2DM). Methods: A MEDLINE (1950-August 2014) literature review was performed. All of the literature published as an original clinical trial was included in this review. Conclusions: With an increasing prevalence and incidence of type 2 diabetes mellitus worldwide, there is an apparent need for effective therapeutic strategies to combat this chronic and progressive disease. SGLT2 inhibitors offer this potential. Recently approved agents (canagliflozin, dapagliflozin and empagliflozin) have shown significant promise as mono- and add-on therapy to current glucose-lowering regimens that may not otherwise be providing sufficient glycemic control in T2DM patients.

28. **A.J. Scheen[86] et al.,**Sodium-glucose cotransporter type 2 (SGLT-2) inhibitors (canagliflozin, dapagliflozin, empagliflozin) are new glucose-lowering agents that exert their therapeutic activity independently of insulin by facilitating glucose excretion through the kidneys. However, this simple renal mechanism that results in sustained glucose urinary loss leads to more complex indirect metabolic effects. First, by reduction of chronic hyperglycaemia and attenuation of glucose toxicity, SGLT-2 inhibitors can improve both insulin secretion by beta cells and peripheral tissue insulin sensitivity. In the case of canagliflozin, because of low-potency SGLT1 inhibition, a non-renal (intestinal)

effect may also be considered, which may contribute to better control of postprandial hyperglycaemia, although this contribution remains to be better analyzed in humans. Second, chronic glucose loss most probably leads to compensatory mechanisms. One of them, although not well evidenced in humans, might involve an increase in energy intake, an effect that may limit weight loss in the long run. Another could be an increase in endogenous glucose production, most probably driven by increased glucagon secretion, which may somewhat attenuate the glucose lowering effect. Nevertheless, despite these compensatory mechanisms and most probably because of the positive effects of the reduction in glucotoxicity, SGLT-2 inhibitors exert clinically relevant glucose-lowering activity while promoting weight loss, a unique dual effect among oral antidiabetic agents. Furthermore, the combination of SGLT-2 inhibitors with other drugs that either have anorectic effects (such as incretin-based therapies) or reduce hepatic glucose output (like metformin) and, thus, may dampen these two compensatory mechanisms appears appealing for the management of type 2 diabetes mellitus.

29. **Muhammad A Abdul-Ghani[87] et al.,**Hyperglycemia plays an important role in the pathogenesis of type 2 diabetes mellitus, i.e., glucotoxicity, and it also is the major risk factor for microvascular complications. Thus, effective glycemic control will not only reduce the incidence of microvascular complications but also correct some of the metabolic abnormalities that contribute to the progression of the disease. Achieving durable tight glycemic control is challenging because of progressive β-cell failure and is hampered by increased frequency of side effects, e.g., hypoglycemia and weight gain. Most recently, inhibitors of the renal sodium-glucose cotransporter have been developed to produce glycosuria and reduce the plasma glucose concentration. These oral antidiabetic agents have the potential to improve glycemic control while avoiding hypoglycemia, to correct the glucotoxicity, and to promote weight loss.

30. **Singh AK[88] et al.,**Sodium-glucose co-transporter-2 inhibitors (SGLT-2i) are newly approved class of oral anti-diabetic drugs, in the treatment of type 2 diabetes, which reduces blood glucose through glucouresis via the kidney, independent, and irrespective of available pancreatic beta-cells. Studies conducted across their clinical development program found, a modest reduction in glycated hemoglobin ranging from -0.5 to -0.8%, without any significant hypoglycemia. Moreover, head-to-head studies versus active comparators yielded comparable efficacy. Interestingly, weight and blood pressure reduction were additionally observed, which was not only consistent but significantly

superior to active comparators, including metformin, sulfonylureas, and dipeptydylpeptide-4 inhibitors. Indeed, these additional properties makes this class a promising oral anti-diabetic drug. Surprisingly, a potentially fatal unwanted side effect of diabetic ketoacidosis has been noted with its widespread use.

31. **Andrew Ahmann[89] et al.,**Type 2 diabetes mellitus (T2DM) management is complex, with few patients successfully achieving recommended glycemic targets with monotherapy, most progressing to combination therapy, and many eventually requiring insulin. Sodium glucose cotransporter 2 (SGLT2) inhibitors are an emerging class of antidiabetes agents with an insulin-independent mechanism of action, making them suitable for use in combination with any other class of antidiabetes agents, including insulin. This review evaluates a 78-week, randomized, double-blind, placebo-controlled trial investigating the impact of empagliflozin, an SGLT2 inhibitor, as add-on to basal insulin in patients with inadequate glycemic control on basal insulin, with or without metformin and/or a sulfonylurea. Empagliflozin added on to basal insulin resulted in significant and sustained reductions in glycated hemoglobin (HbA1c) levels compared with placebo. Empagliflozin has previously been shown to induce weight loss, and was associated with sustained weight loss in this study. This combination therapy was well tolerated, with similar levels of hypoglycemic adverse events in the empagliflozin and placebo groups over the 78-week treatment period. Urinary tract infections and genital infections, side effects associated with SGLT2 inhibitors, were reported more commonly in the empagliflozin group; however, such events led to treatment discontinuation in very few patients. These findings suggest that, with their complementary mechanisms of action, empagliflozin added on to basal insulin may be a useful treatment option in patients on basal insulin who need additional glycemic control without weight gain.

32. **William L Baker[89] et al**., Sodium-glucose co-transporter 2 (SGLT2) inhibitors represent a new class of antihyperglycemic agents that block renal sodium and glucose reabsorption and may reduce blood pressure (BP). We assessed the BP lowering ability of these agents using meta-analytic techniques. We included fully published randomized controlled trials (RCTs) that evaluated SGLT2 inhibitors in patients with type-2 diabetes mellitus and reported change in systolic and/or diastolic BP. Subgroup analyses were performed for placebo-controlled trials and those with active controls. We also conducted meta-regression to assess for a dose-response effect, and whether baseline BP, changes in body weight, heart rate, and hematocrit were associated with the BP effects. Results Twenty seven RCTs (n=12,960 participants) were included. SGLT2 inhibitors significantly reduced both SBP (weighted mean difference

[WMD] -4.0 mmHg, 95% CI -4.4 to -3.5) and DBP (WMD -1.6 mmHg, 95% CI -1.9 to -1.3) from baseline. Only canagliflozin had a significant dose-response relationship with SBP (p=0.008). Significant reductions in body weight and hematocrit were seen with the SGLTs. SGLTs had no significant effect on the incidence of orthostatic hypotension (p>0.05). Sodium-glucose co-transporter 2 inhibitors significantly reduce BP in patients with type 2 diabetes.

33.**Anna Solini[90] et al.,**In the last ten years, knowledge on pathophysiology of type 2 diabetes (T2DM) has significantly increased, with multiple failures (decreased incretin effect, increased lipolysis, increased glucagon secretion, neurotransmitters dysfunction) recognized as important contributors, together with decreased insulin secretion and reduced peripheral glucose uptake. As a consequence, the pharmacologic therapy of T2DM has been progressively enriched by several novel classes of drugs, trying to overcome these defects. SGLT2 inhibitors, framing the kidney in a different scenario, not as site of a harmful disease complication, but rather as the means to correct hyperglycemia and fight the disease. This review aims to offer a short, updated overview of the role of these compounds in the treatment of T2DM, focusing on efficacy, ancillary albeit relevant clinical effects, safety, potential cardiovascular protection, positioning in common therapeutic algorithms.

34.**Aurora Merovci[91] et al.,** β-Cell dysfunction is a core defect in T2DM, and chronic, sustained hyperglycemia has been implicated in progressive β-cell failure, ie, glucotoxicity. The aim of the present study was to examine the effect of lowering the plasma glucose concentration with dapagliflozin, a glucosuric agent, on β-cell function in T2DM individuals. Research design and methods: Twenty-four subjects with T2DM received dapagliflozin (n = 16) or placebo (n = 8) for 2 weeks, and a 75-g oral glucose tolerance test (OGTT) and insulin clamp were performed before and after treatment. Plasma glucose, insulin, and C-peptide concentrations were measured during the OGTT. Results: Dapagliflozin significantly lowered both the fasting and 2-hour plasma glucose concentrations and the incremental area under the plasma glucose concentration curve (ΔG0-120) during OGTT by -33 ± 5 mg/dL, -73 ± 9 mg/dL, and -60 ± 12 mg/dL · min, respectively, compared to -13 ± 9, -33 ± 13, and -18 ± 9 reductions in placebo-treated subjects (both P < .01). The incremental area under the plasma C-peptide concentration curve tended to increase in dapagliflozin-treated subjects, whereas it did not change in placebo-treated subjects. Thus, ΔC-Pep0-120/ΔG0-120 increased significantly in dapagliflozin-treated subjects, whereas it did not change in placebo-treated subjects (0.019 ± 0.005 vs 0.002 ± 0.006; P < .01). Dapagliflozin significantly improved whole-body insulin sensitivity (insulin clamp). Thus, β-cell function, measured as ΔC-Pep0-120/ ΔG0-120 ÷ insulin resistance, increased by 2-fold (P < .01) in dapagliflozin-treated vs placebo-treated subjects. Lowering the plasma glucose

concentration with dapagliflozin markedly improves β-cell function, providing strong support in man for the glucotoxic effect of hyperglycemia on β-cell function.

35. **Krzysztof Strojek[92] et al.,** Progressive deterioration of glycaemic control in type 2 diabetes mellitus (T2DM) often requires treatment intensification. Dapagliflozin increases urinary glucose excretion by selective inhibition of renal sodium-glucose co transporter 2 (SGLT2). We assessed the efficacy, safety and tolerability of dapagliflozin added to glimepiride in patients with uncontrolled T2DM. This 24-week, randomized, double-blind, placebo-controlled, parallel-group, international, multicentre trial enrolled patients with uncontrolled T2DM [haemoglobin A1c (HbA1c) 7-10%] receiving sulphonyl urea mono therapy. Adult patients (n = 597) were randomly assigned to placebo or dapagliflozin (2.5, 5 or 10 mg/day) added to open-label glimepiride 4 mg/day for 24 weeks. Primary endpoint was HbA1c mean change from baseline at 24 weeks. Secondary endpoints included change in body weight and other glycaemic parameters. At 24 weeks, HbA1c adjusted mean changes from baseline for placebo versus dapagliflozin 2.5/5/10 mg groups were -0.13 versus -0.58, -0.63, -0.82%, respectively (all $p < 0.0001$ vs. placebo by Dunnett's procedure). Corresponding body weight and fasting plasma glucose values were -0.72, -1.18, -1.56, -2.26 kg and -0.11, -0.93, -1.18, -1.58 mmol/l, respectively. In placebo versus dapagliflozin groups, serious adverse events were 4.8 versus 6.0-7.1%; hypoglycaemic events 4.8 versus 7.1-7.9%; events suggestive of genital infection 0.7 versus 3.9-6.6%; and events suggestive of urinary tract infection 6.2 versus 3.9-6.9%. No kidney infections were reported. Dapagliflozin added to glimepiride in patients with T2DM uncontrolled on sulphonylurea monotherapy significantly improved HbA1c, reduced weight and was generally well tolerated, although events suggestive of genital infections were reported more often in patients receiving dapagliflozin.

36. **B Haaset[93] et al.,** Renal sodium-linked glucose transporter 2 inhibitors are new antidiabetic drugs with an insulin-independent mechanism of action. They pose one remarkable advantage compared with already established antidiabetics: increasing urinary glucose excretion without inducing hypoglycaemia, thereby promoting body weight reduction due to loss of ~300 kcal per day. This review focuses on canagliflozin, which was the first successful compound of this class to be approved by both the US Food and Drug Administration and the European Medicines Agency in 2013. Clinical

trials showed promising results: enhancing glycaemic control was paralleled by reducing body weight and systolic and diastolic blood pressure. Nevertheless, some safety concerns remain, such as genital mycotic infections, urinary tract infections and cardiovascular risks in vulnerable patients, which will be closely monitored in several post-authorization safety studies.

37.**David Polidori[94] et al.,**In rodent models of diabetes, treatment with sodium glucose co-transporter 2 (SGLT2) inhibitors improves beta cell function. This analysis assessed the effects of the SGLT2 inhibitor, canagliflozin, on model-based measures of beta cell function in patients with type 2 diabetes. Data from three Phase 3 studies were analysed, in which: (Study 1) canagliflozin 100 and 300 mg were compared with placebo as monotherapy for 26 weeks; (Study 2) canagliflozin 100 and 300 mg were compared with placebo as add-on to metformin + sulfonylurea for 26 weeks; or (Study 3) canagliflozin 300 mg was compared with sitagliptin 100 mg as add-on to metformin + sulfonylurea for 52 weeks. In each study, a subset of patients was given mixed-meal tolerance tests at baseline and study endpoint, and model-based beta cell function parameters were calculated from plasma glucose and C-peptide. In Studies 1 and 2, both canagliflozin doses increased beta cell glucose sensitivity compared with placebo. Placebo-subtracted least squares mean (LSM) (SEM) changes were 23 (9) and 18 (9) pmol min(-1) m(-2) (mmol/l)(-1) with canagliflozin 100 and 300 mg, respectively ($p < 0.002$, Study 1), and 16 (8) and 10 (9) pmol min(-1) m(-2) (mmol/l)(-1) ($p < 0.02$, Study 2). In Study 3, beta cell glucose sensitivity was minimally affected, but the insulin secretion rate at 9 mmol/l glucose increased to similar degrees from baseline with canagliflozin and sitagliptin [LSM (SEM) changes 38 (8) and 28 (9) pmol min(-1) m(-2), respectively; $p < 0.05$ for both].

38. **Robert R Henry[95] et al.,**This randomized, double-blind, placebo-controlled parallel-group study assessed the effects of sodium glucose cotransporter 2 inhibition by dapagliflozin on insulin sensitivity and secretion in subjects with type 2 diabetes mellitus (T2DM), who had inadequate glycemic control with metformin Forty-four subjects were randomized to receive dapagliflozin 5 mg or matching placebo once daily for 12 weeks. Subjects continued stable doses of antidiabetes medication throughout the study. Insulin sensitivity was assessed by measuring the glucose disappearance rate (GDR) during the last 40 min of a 5-h hyperinsulinemic, euglycemic clamp. Insulin secretion was determined as the acute insulin response to glucose (AIRg) during the first 10 min of a frequently sampled intravenous glucose tolerance test. Where noted, data were adjusted for baseline values and background antidiabetes medication. Results: An adjusted mean increase from baseline in GDR (last observation carried

forward), at Week 12, was observed with dapagliflozin (7.98%) versus a decrease with placebo (-9.99%). The 19.97% (95% confidence interval 5.75-36.10) difference in GDR versus placebo was statistically significant (P=0.0059). A change from baseline in adjusted mean AIRg of 15.39 mU/L min was observed with dapagliflozin at Week 12, versus -12.73 mU/L min with placebo (P=0.0598). Over 12 weeks, numerical reductions from baseline in glycosylated hemoglobin (HbA1c), fasting plasma glucose, and body weight were observed with dapagliflozin (-0.38%, -0.39 mmol/L, and -1.58%, respectively) versus slight numerical increases with placebo (0.03%, 0.26 mmol/L, and 0.62%, respectively). In patients with T2DM and inadequate glycemic control, dapagliflozin treatment improved insulin sensitivity in the setting of reductions in HbA1c and weight.

39.**Luke Norton[96] et al.,**Hyperglycemia plays an important role in the pathogenesis of type 2 diabetes mellitus, i.e., glucotoxicity, and it also is the major risk factor for microvascular complications. Thus, effective glycemic control will not only reduce the incidence of microvascular complications but also correct some of the metabolic abnormalities that contribute to the progression of the disease. Achieving durable tight glycemic control is challenging because of progressive β-cell failure and is hampered by increased frequency of side effects, e.g., hypoglycemia and weight gain. Most recently, inhibitors of the renal sodium-glucose cotransporter have been developed to produce glucosuria and reduce the plasma glucose concentration. These oral antidiabetic agents have the potential to improve glycemic control while avoiding hypoglycemia, to correct the glucotoxicity, and to promote weight loss.

40.**André J Scheen[97] et al.,**Empagliflozin is an orally active, potent and selective inhibitor of sodium glucose co-transporter 2 (SGLT2), currently in clinical development to improve glycaemic control in adults with type 2 diabetes mellitus (T2DM). SGLT2 inhibitors, including empagliflozin, are the first pharmacological class of antidiabetes agents to target the kidney in order to remove excess glucose from the body and, thus, offer new options for T2DM management. SGLT2 inhibitors exert their effects independently of insulin. Following single and multiple oral doses (0.5-800 mg), empagliflozin was rapidly absorbed and reached peak plasma concentrations after approximately 1.33-3.0 h, before showing a biphasic decline. The mean terminal half-life ranged from 5.6 to 13.1 h in single rising-dose studies, and from 10.3 to 18.8 h in multiple-dose studies. Following multiple oral doses, increases in exposure were dose-proportional and trough concentrations remained constant after day 6, indicating a steady state had been reached. Oral clearance at steady state was

similar to corresponding single-dose values, suggesting linear pharmacokinetics with respect to time. No clinically relevant alterations in pharmacokinetics were observed in mild to severe hepatic impairment, or in mild to severe renal impairment and end-stage renal disease. Clinical studies did not reveal any relevant drug-drug interactions with several other drugs commonly prescribed to patients with T2DM, including warfarin. Urinary glucose excretion (UGE) rates were higher with empagliflozin versus placebo and increased with dose, but no relevant impact on 24-h urine volume was observed. Increased UGE resulted in proportional reductions in fasting plasma glucose and mean daily glucose concentrations.

41.**Chiara Ghezzi[98] et al.,**SGLT2 inhibitors are a new class of drugs that have been recently developed to treat type II diabetes. They lower glucose levels by inhibiting the renal Na+/glucose cotransporter SGLT2, thereby increasing the amount of glucose excreted in the urine. Pharmacodynamics studies have raised questions about how these inhibitors reach SGLT2 in the brush border membrane of the S1 and S2 segments of the renal proximal tubule: are these drugs filtered by the glomerulus and act extracellularly, or do they enter the cell and act intracellularly? Inhibition of SGLT2 activity (Na+/glucose currents) was determined using the whole-cell patch clamp that allows controlling the composition of both the extracellular and intracellular solutions. We compared the results to those obtained using the nonselective SGLT inhibitor phlorizin, Our results showed that SGLT2 transport (IC50 2 nmol/L) ineffective from the intracellular compartment at both low (5 mmol/L) and high (150 mmol/L) intracellular NaCl concentrations. We conclude that SGLT2 from the extracellular side of the plasma membrane, suggesting that it is filtered from the blood through the glomerulus and acts from within the tubule lumen.

42.**André J[99] et al.,** Inhibitors of sodium-glucose cotransporters type 2 (SGLT2) reduce hyperglycaemia by decreasing renal glucose threshold and thereby increasing urinary glucose excretion. They are proposed as a novel approach for the management of type 2 diabetes mellitus. They have proven their efficacy in reducing glycated haemoglobin, without inducing hypoglycaemia, as monotherapy or in combination with various other glucose-lowering agents, with the add-on value of promoting some weight loss and lowering arterial blood pressure. As they may be used concomitantly with many other drugs, we review the potential drug-drug interactions (DDIs) regarding the three leaders in the class (dapagliglozin, canagliflozin and empagliflozin). Most of the available studies were performed in healthy volunteers and have assessed the pharmacokinetic interferences with a single administration of the SGLT2 inhibitor. The exposure [assessed by peak plasma concentrations (C max) and area under the concentration-time curve (AUC)] to each SGLT2 inhibitor tested was not significantly influenced by the concomitant administration of other

glucose-lowering agents or cardiovascular agents commonly used in patients with type 2 diabetes. Reciprocally, these medications did not influence the pharmacokinetic parameters of dapagliflozin, canagliflozin or empagliflozin. Some modest changes were not considered as clinically relevant. However, drugs that could specifically interfere with the metabolic pathways of SGLT2 inhibitors [rifampicin, inhibitors or inducers of uridine diphosphate-glucuronosyltransferase (UGT)] may result in significant changes in the exposure of SGLT2 inhibitors, as shown for dapagliflozin and canagliflozin. Potential DDIs in patients with type 2 diabetes receiving chronic treatment with an SGLT2 inhibitor deserve further attention, especially in individuals treated with several medications or in more fragile patients with hepatic and/or renal impairment.

43.**David Polidori[100] et al.,**Canagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, is also a low-potency SGLT1 inhibitor. This study tested the hypothesis that intestinal canagliflozin levels postdose are sufficiently high to transiently inhibit intestinal SGLT1, thereby delaying intestinal glucose absorption.This two-period, crossover study evaluated effects of canagliflozin on intestinal glucose absorption in 20 healthy subjects using a dual-tracer method. Placebo or canagliflozin 300 mg was given 20 min before a 600-kcal mixed-meal tolerance test. Plasma glucose, (3)H-glucose, (14)C-glucose, and insulin were measured frequently for 6 h to calculate rates of appearance of oral glucose (R(a)O) in plasma, endogenous glucose production, and glucose disposal. Compared with placebo, canagliflozin treatment reduced postprandial plasma glucose and insulin excursions (incremental 0- to 2-h area under the curve [AUC(0-2h)] reductions of 35% and 43%, respectively; $P < 0.001$ for both), increased 0- to 6-h urinary glucose excretion (UGE(0-6h), 18.2 ± 5.6 vs <0.2 g; $P < 0.001$), and delayed R(a)O. Canagliflozin reduced AUC R(a)O by 31% over 0 to 1 h (geometric means, 264 vs. 381 mg/kg; $P < 0.001$) and by 20% over 0 to 2 h (576 vs. 723 mg/kg; $P = 0.002$). Over 2 to 6 h, canagliflozin increased R(a)O such that total AUC R(a)O over 0 to 6 h was <6% lower versus placebo (960 vs. 1,018 mg/kg; $P = 0.003$). A modest (~10%) reduction in acetaminophen absorption was observed over the first 2 h, but this difference was not sufficient to explain the reduction in R(a)O. Total glucose disposal over 0 to 6 h was similar across groups. Canagliflozin reduces postprandial plasma glucose and insulin by increasing UGE (via renal SGLT2 inhibition) and delaying R(a)O, likely due to intestinal SGLT1 inhibition.

44.**Hideaki Jinnouchi[101] et al.,**We investigated the impact of reduced renal function on 24-h glucose variability in Japanese patients with type 2 diabetes mellitus (T2DM) treated with luseogliflozin. In this double-blind, placebo-controlled, crossover study, 37 Japanese patients with T2DM [glycated hemoglobin (HbA1c) 7.0-10.0%] and estimated glomerular filtration rate

(eGFR) ≥45 mL/min/1.73 m(2) were randomized into two groups in which patients first received luseogliflozin then placebo, or vice versa, for 7 days each. Twenty-four-hour glucose variability was measured on day 7 in each period and was compared among patients divided into three groups according to their baseline eGFR (mL/min/1.73 m(2)): normal (≥90; n = 13; normal group), normal-to-mildly reduced renal function (≥75 to <90; n = 12; normal-mild group), and mild-to-moderately reduced renal function (<75; n = 9; mild-moderate group). Results: The mean [95% confidence interval (CI)] placebo-subtracted 24-h cumulative urinary glucose excretion (g) was 82.1 (72.7, 91.5), 82.5 (73.4, 91.5), and 62.2 (51.2, 73.3); the placebo-subtracted 24-h mean glucose concentration (mg/dL) was -24.39 (-32.53, -16.26), -28.28 (-39.35, -17.22), and -11.53 (-23.93, 0.86); and the placebo-subtracted peak postprandial glucose (mg/dL) was -26.9 (-46.9, -6.9), -38.1 (-59.6, -16.6), and 1.5 (-25.5, 28.4) in the normal, normal-mild, and mild-moderate groups, respectively. The mean lowest glucose concentrations (placebo vs. luseogliflozin, mg/dL) decreased to similar levels in the normal (115.4 vs. 93.4), normal-mild (121.0 vs. 97.9), and mild-moderate (104.0 vs. 91.1) groups. This post hoc subanalysis revealed that although mild-to-moderately reduced renal function attenuated the glucose-lowering effects of luseogliflozin on peak postprandial glucose, it did not attenuate the effects of luseogliflozin on fasting glucose. These findings may explain the smaller increase in urinary glucose excretion in these patients relative to patients with normal renal function or normal-to-moderately reduced renal function.

AIM OF THE STUDY:

To observe the blood sugar lowering and other pleiotropic effects like changes in body weight and BMI, systolic and diastolic BP changes in type 2 diabetes mellitus subjects with the latest anti diabetic agents of the class SGLT2 inhibitors namely Canagliflozin, Dapagliflozin and Empagliflozin over a minimum period of 3 months.

OBJECTIVES:

- To assess the number of hypoglycaemic events.
- To assess the effect on body weight.
- To determine macrovascular complication in type 2 DM
- To compare and assess effect of drugs on type 2 DM and the role in renal protection.

SUBJECTS:

It is decided to recruit 35 subjects of Type 2 DM, male and female, taking any one of the three SGLT2 inhibitors that are available in the indian pharmaceutical market namely canagliflozin, Dapagliflozin and Empagliflozin attending the outpatient services of the Madurai Institute of Diabetes and Endocrine (MIDE) practice and research at 89A,East veli street and 96,Nakkeerar street, Madurai.

INCLUSION CRITERIA:

Subjects should be suffering from Type 2 Diabetes Mellitus as per the usual clinical and laboratory criteria that is followed at MIDE. They should all be adults above the age 18 years. Even though it is only an observational study informed consent was obtained from all subjects.

Most of the patients were already on one or two insulin secretagogues and one or two insulin sensitizers. Somewhere on alpha glucosidase inhibitors. Subjects with cardiovascular risks were on appropriate anti platelet therapy and any one statin, hypertensives were on appropriate anti hypertensives. No dosage adjustments or alterations of these drugs were made during the 3 months study period.

EXCLUSION CRITERIA:

Drug naive patients who were not on adequate doses of insulin secretagogues or sensitizers, subjects who had moderate to severe renal failure, mild, moderate, severe liver disease and acute coronary syndrome, infarct, stroke or ketoacidosis or suffering from any acute or chronic infections.

METHODOLOGY

In this observational study we did not disturb the routine of the patients or the physicians in the clinic. We tried to collect atleast 10 subjects in each group with a total of 30 subjects in all. we recruited 35 subjects in all out of which 6 were excluded due to reasons of inadequate length of treatment. The parameters which we studied with a view to compare head to head the three agents are body weight, BMI, systolic and diastolic and 2 hours post prandial blood sugar values

Clinical evaluation regarding age, gender, duration of disease, age onset, any other complication and family history evaluation were done in all the cases.

Patient were received after the treatment measurement. The observed parameter were analysed. Discussion was held with Diabetologist for the interpretation of collected data.

The efficacy of each group was determined and conclusion was drawn.

Finally patient were counselled regarding the importance of strict glycemic control attained by diabetic diet & regular exercise with proper drug treatment.

COLLECTION AND COMPILATION OF DATA:

Source of data used:

Patient interview

Patient case notes

Treatment chart

CALCULATION OF BODY MASS INDEX (BMI):

BMI can be calculated by measuring the height and weight of the person.

$$\textbf{BMI=Weight (kg)/height}^2\ \textbf{(cm}^2\textbf{)}$$

BMI of 10-18.5 shows underweight;18.5-23 shows normal;23-27.5 shows over weight and greater than 27.5 shows obese.

STATISTICAL ANALYSIS:

STATISTICAL TOOLS:

The information collected regarding all the selected cases were recorded in a master chart. Data analysis was done with the help of graph pad instat. Using this software mean, standard deviation, and P values were calculated. P value less than 0.05 is taken to denote significant relationship.

Statistical method used is the student T test for paired samples.

AN OBSERVATIONAL STUDY ON THE COMPARATIVE EFFICACY AND SAFETY OF CANAGLIIFLOZIN, DAPAGLIFLOZIN AND EMPAGLIFLOZIN IN TYPE 2 DM

Table 1:AGE DISTRIBUTION

DRUG	30-39	40-49	50-59	60-69	70-79	80-89
CANAGLIFLOZIN	0	6	2	3	1	0
DAPAGLIFLOZIN	1	1	2	3	1	1
EMPAGLIFLOZIN	1	2	3	2	0	0

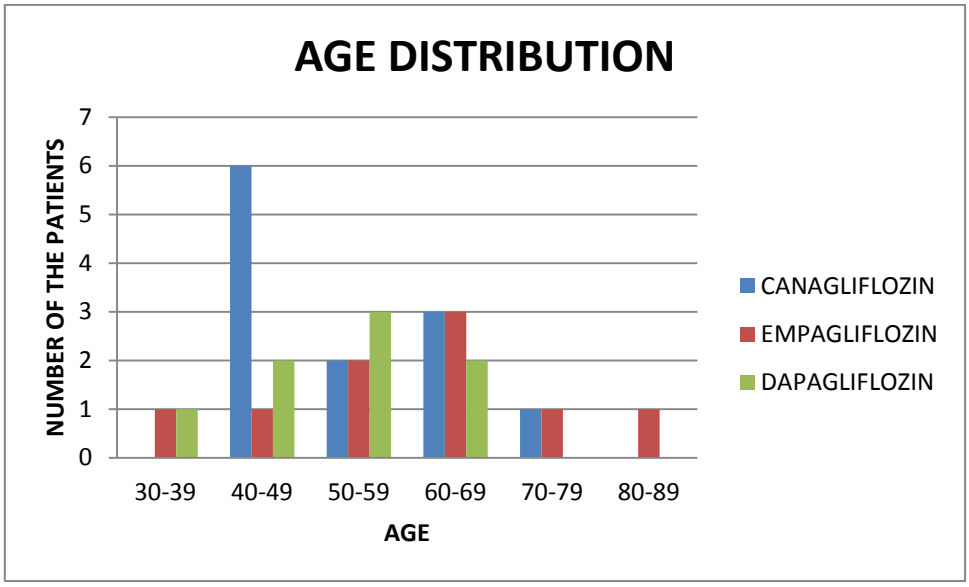
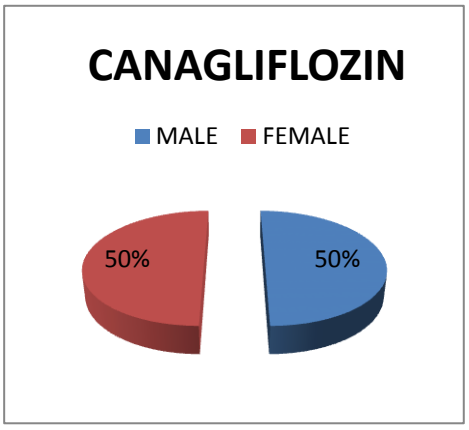
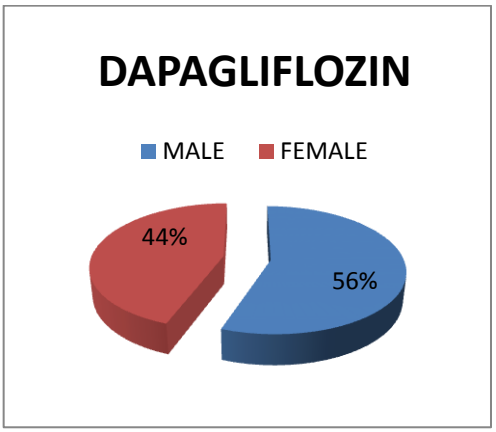


Table 2:SEX DISTRIBUTION

SEX	CANAGLIFLOZIN	DAPAGLIFLOZIN	EMPAGLIFLOZIN
MALE	6	5	2
FEMALE	6	4	6





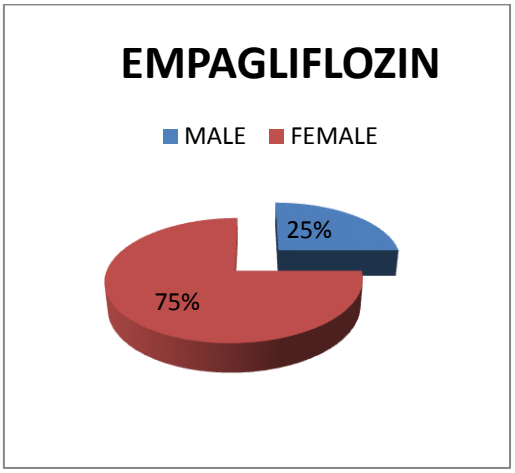
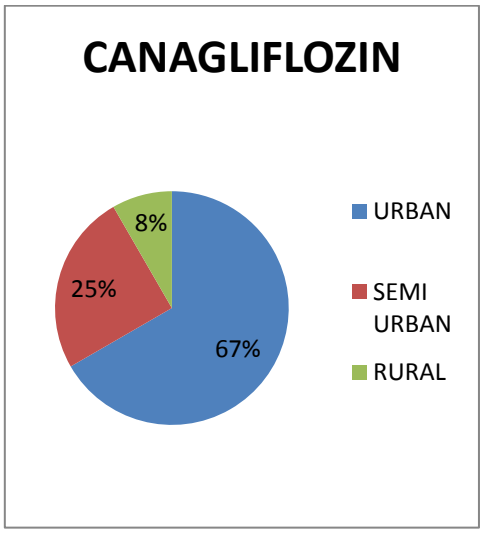
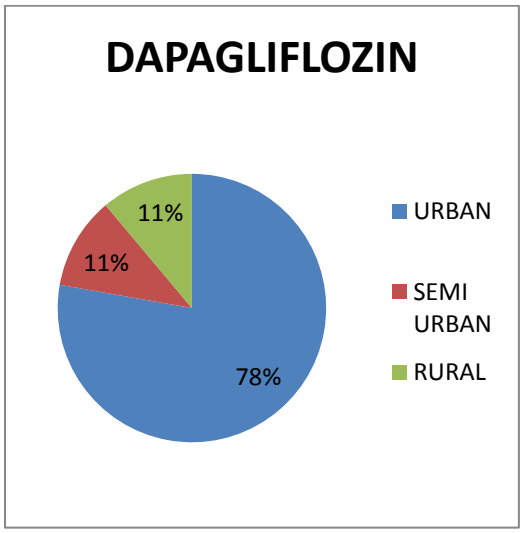


Table 3: RESIDENCE

AREA	CANAGLIFLOZIN	DAPAGLIFLOZIN	EMPAGLIFLOZIN
URBAN	8	7	6
SEMI URABAN	3	1	2
RURAL	1	1	0





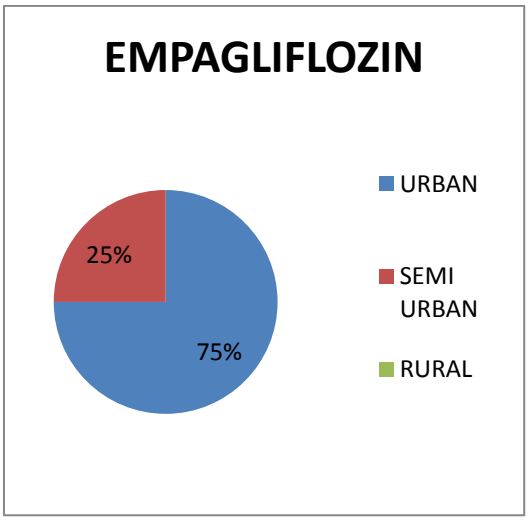
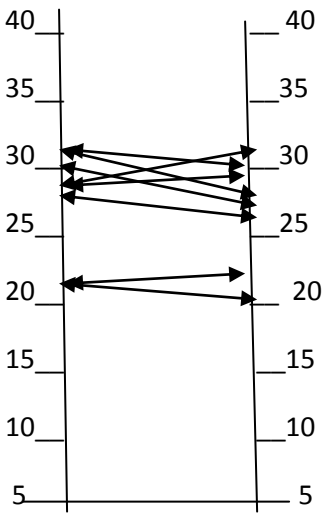


Table 4:BMI BEFORE AND AFTER THERPY

CANAGLIFLOZIN		DAPAGLIFLOZIN		EMPAGLIFLOZIN	
BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER
30.3	27.1	27.1	25.3	30.8	27.6
28	26.4	22.2	22.2	27.3	27.3
22.5	20.4	27.8	26.1	26.7	24
29	32	29.2	29.2	23.6	22.7
30	27.9	23.7	23.7	30.4	28.9
28.8	29.24	21.8	22.4	26.2	26.2
28.9	27.8	20.9	20.9	30.2	25.1
28.7	27.7	28.7	26.9	24.5	24.5
29.1	27.4	29	26.7		
30.4	27.8				
30.9	27.9				
21.6	21				

CANAGLIFLOZIN



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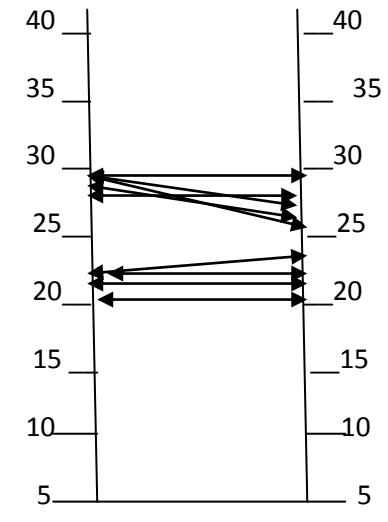
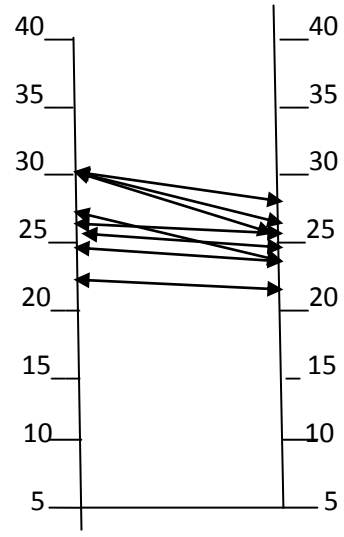


EMPAGLIFLOZIN



MEAN	28.18	26.88	25.6	24.82	27.46	25.78
SD	2.99	3.20	3.408	2.698	2.755	2.080

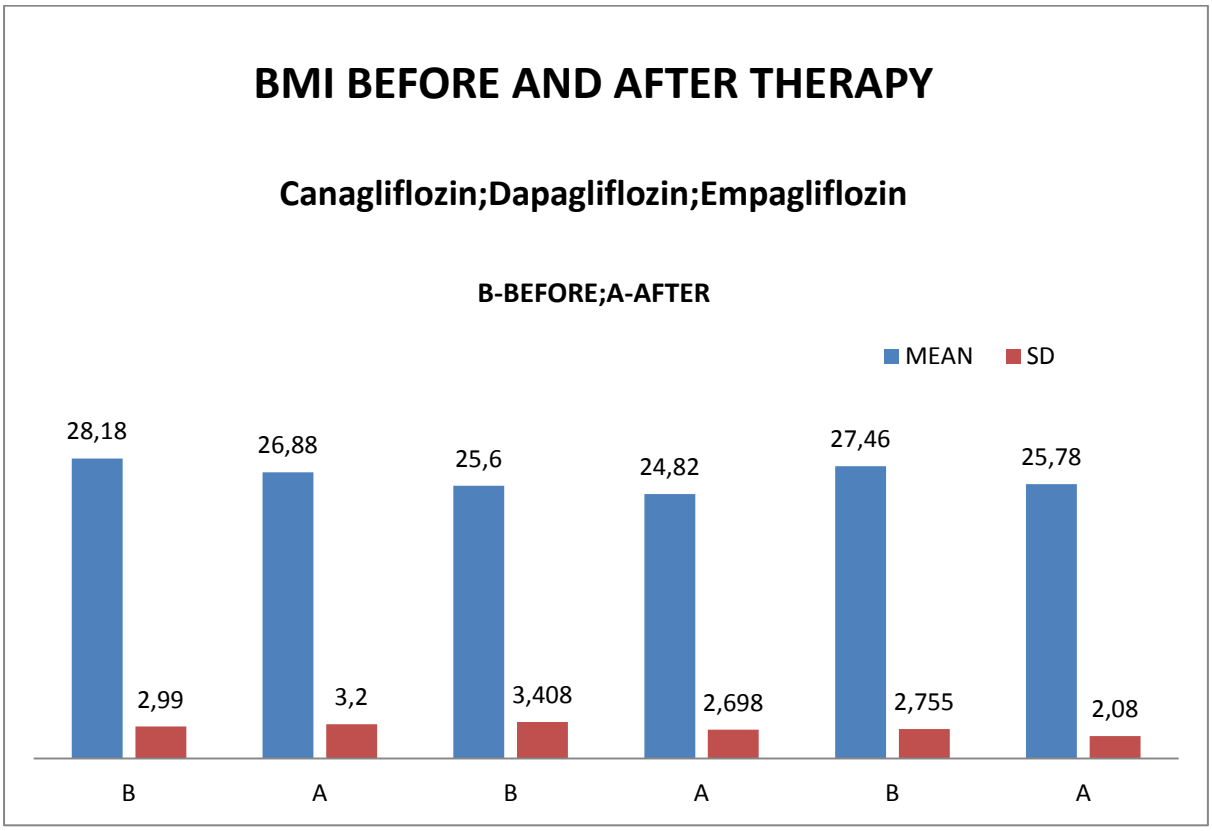
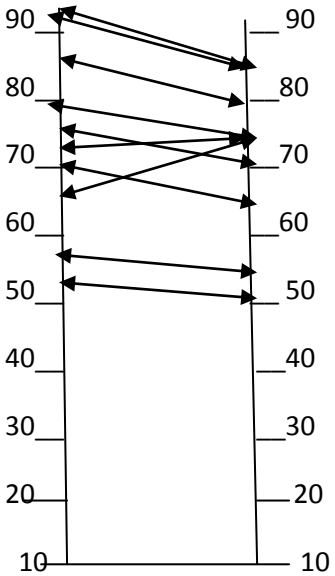


Table 5:BODY WEIGHT BEFORE AND AFTER THERAPY

CANAGLIFLOZIN		DAPAGLIFLOZIN		EMPAGLIFLOZIN	
BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER
96	86	73	68	85	76
70	66	60	62	61	61
54	49	65	61	70	63
67	74	63	63	49	47
80	74	68	68	63	60
72	73	56	58	82	82
75	72	49	49	71	59
57	55	81	76	72	72
85	80	68	62.4		
93	85				
82	74				
67	65				

CANAGLIFLOZIN



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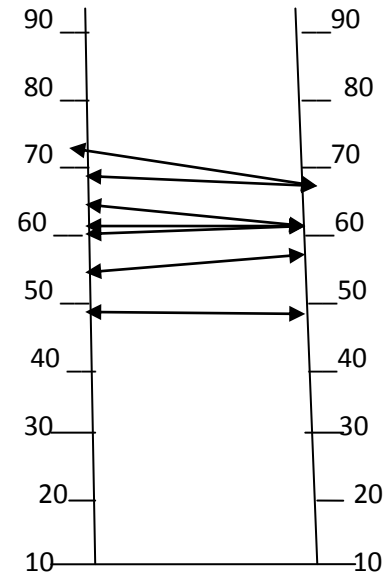

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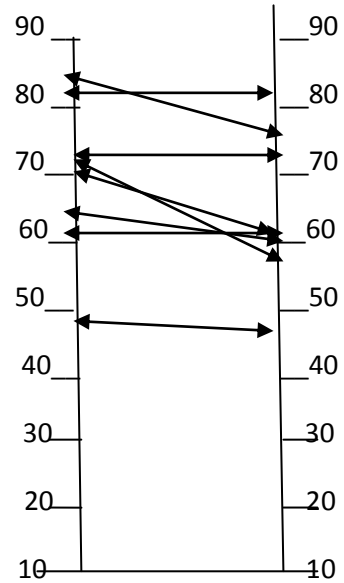
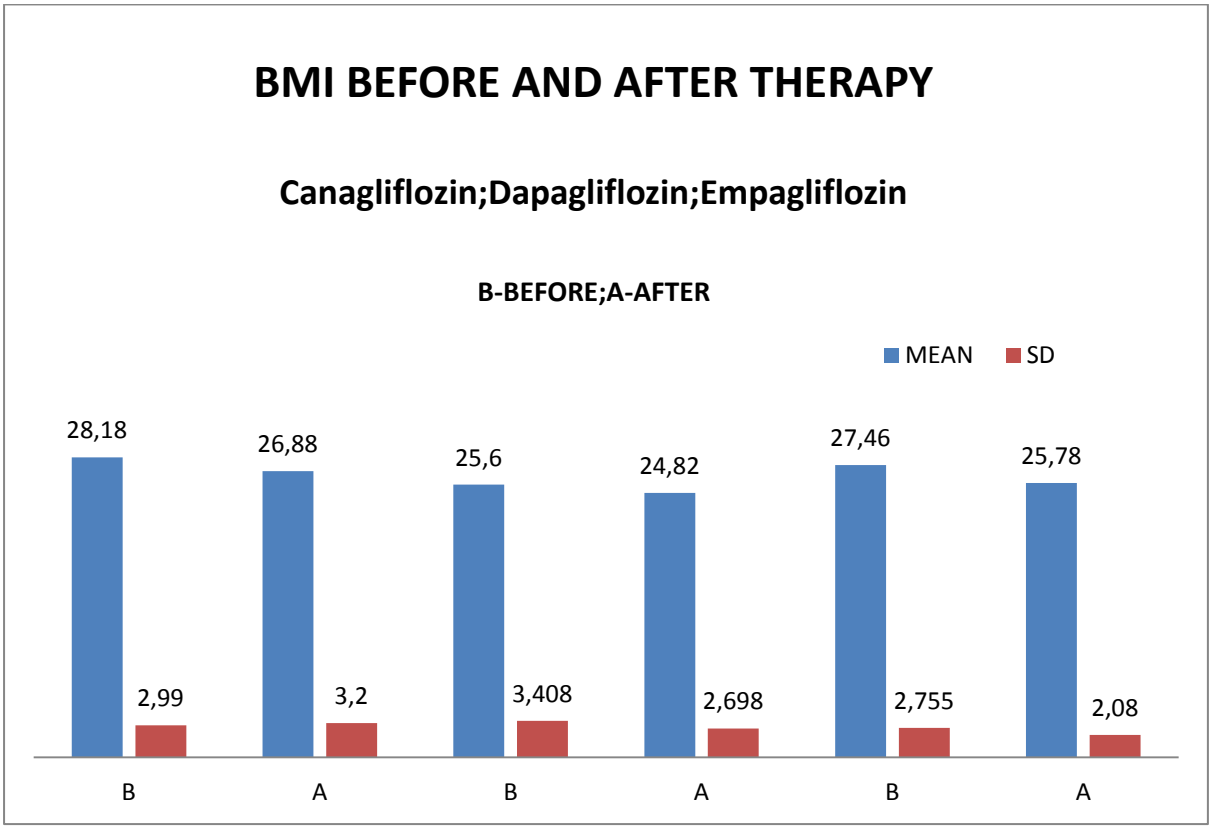
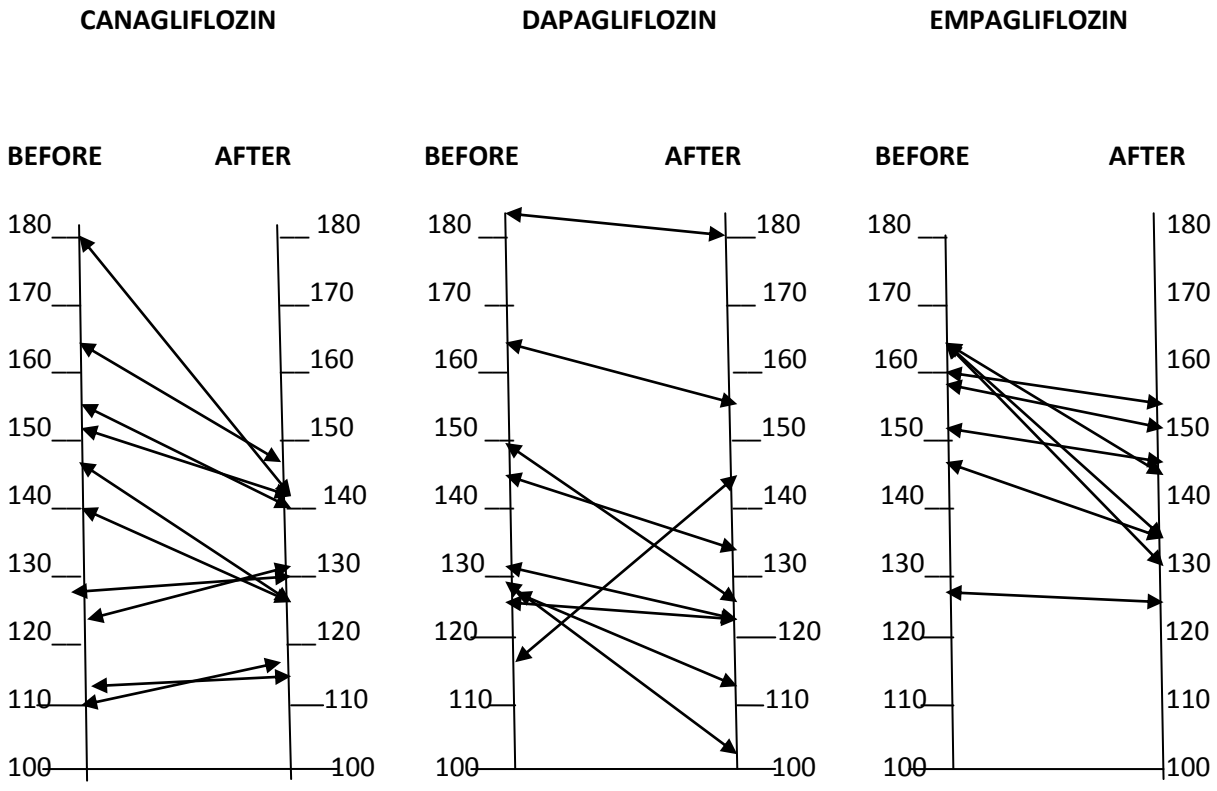


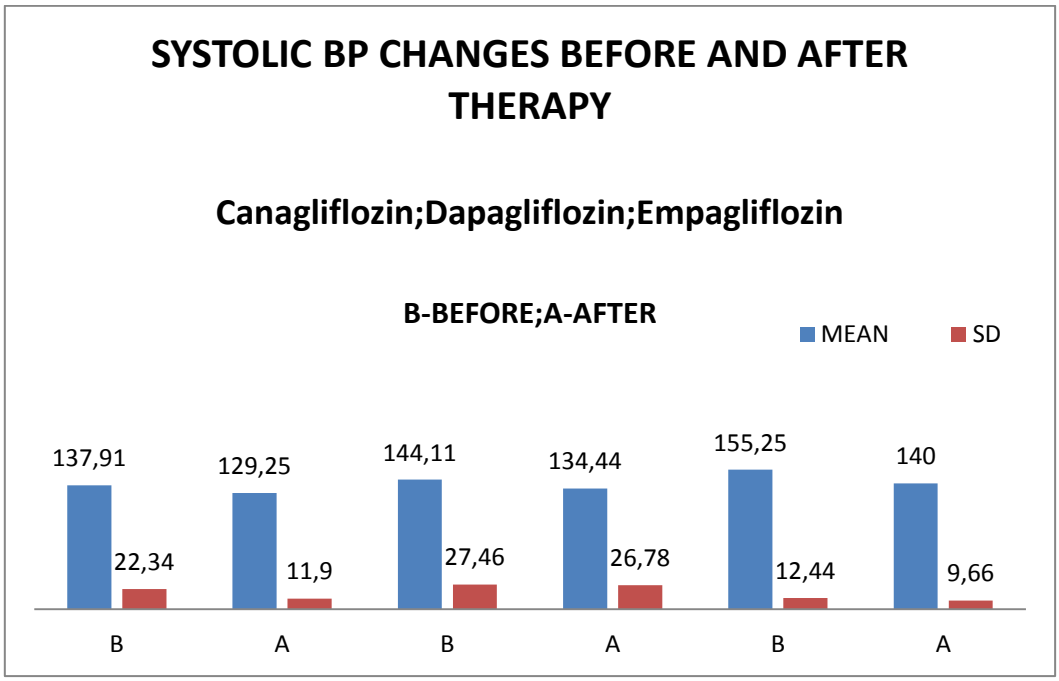


MEAN	74.83	71.08	64.77	63.04	69.12	65
SD	13.02	11.01	9.37	7.46	11.58	11.10

Table 6:SYSTOLIC BP CHANGES BEFORE AND AFTER THERAPY

CANAGLIFLOZIN		DAPAGLIFLOZIN		EMPAGLIFLOZIN	
BEFORE mm/hg	AFTER mm/hg	BEFORE mm/hg	AFTER mm/hg	BEFORE mm/hg	AFTER mm/hg
122	131	165	156	165	134
180	142	145	133	128	128
147	126	125	122	164	142
153	143	206	192	149	135
140	125	131	123	160	154
114	120	128	112	153	147
156	140	117	144	158	150
110	118	150	125	165	130
120	111	130	103		
165	145				
120	120				
128	130				

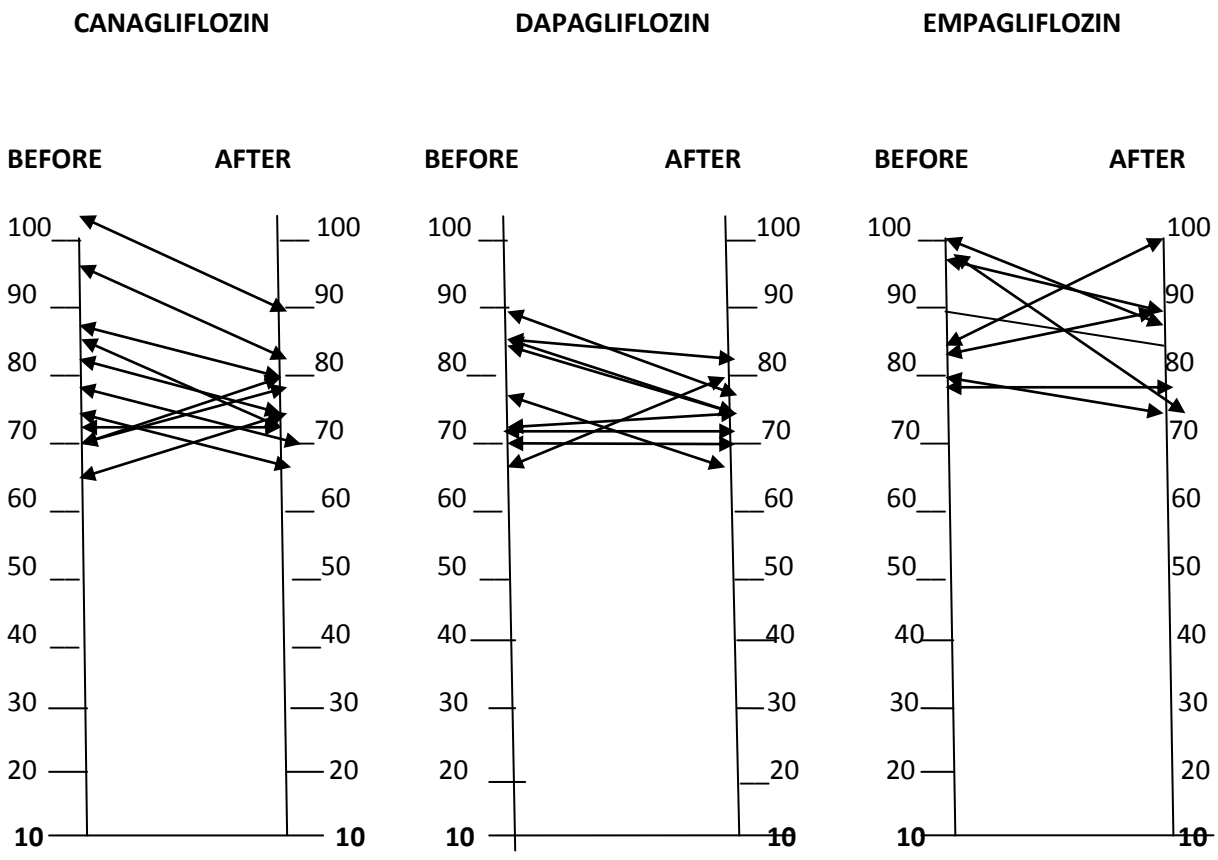


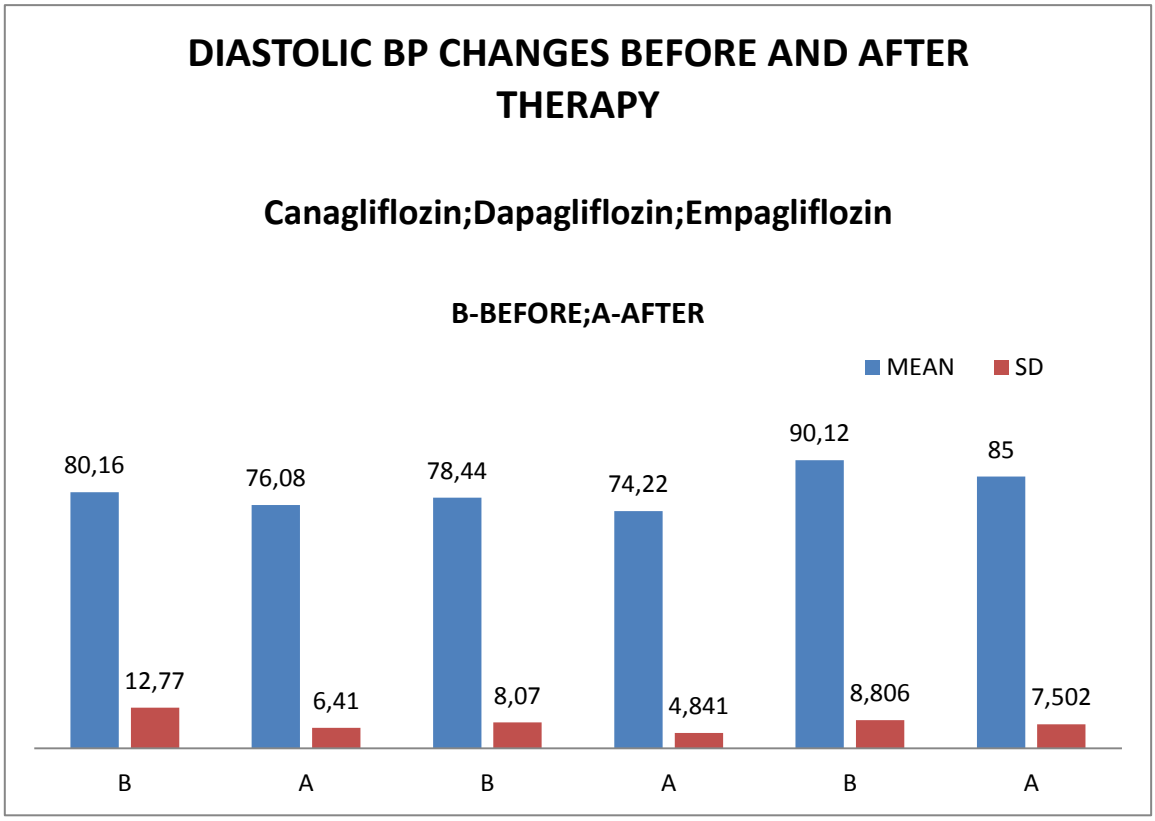


MEAN	137.91	129.25	144.11	134.44	155.25	140
SD	22.34	11.19	27.46	26.78	12.44	9.66

Table 7:DIASTOLIC BP CHANGES BEFORE AND AFTER THERAPY

CANAGLIFLOZIN		DAPAGLIFLOZIN		EMPAGLIFLOZIN	
BEFORE mm/hg	AFTER mm/hg	BEFORE mm/hg	AFTER mm/hg	BEFORE mm/hg	AFTER mm/hg
65	76	72	74	98	84
98	73	72	72	79	79
7+	67	70	70	103	85
84	72	86	83	87	80
70	79	85	75	86	100
71	73	85	73	80	76
108	90	69	80	98	90
70	80	77	67	90	86
78	70	90	74		
87	78				
84	70				
71	75				

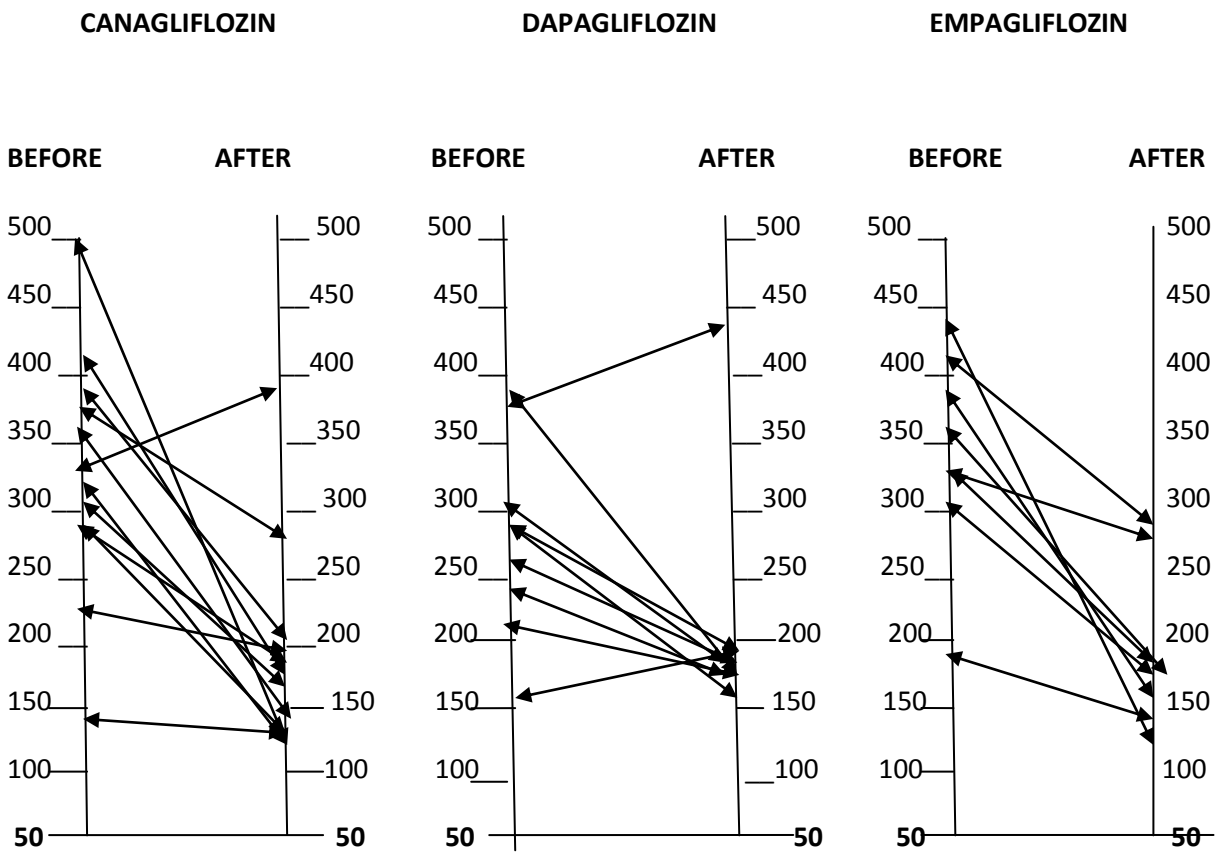


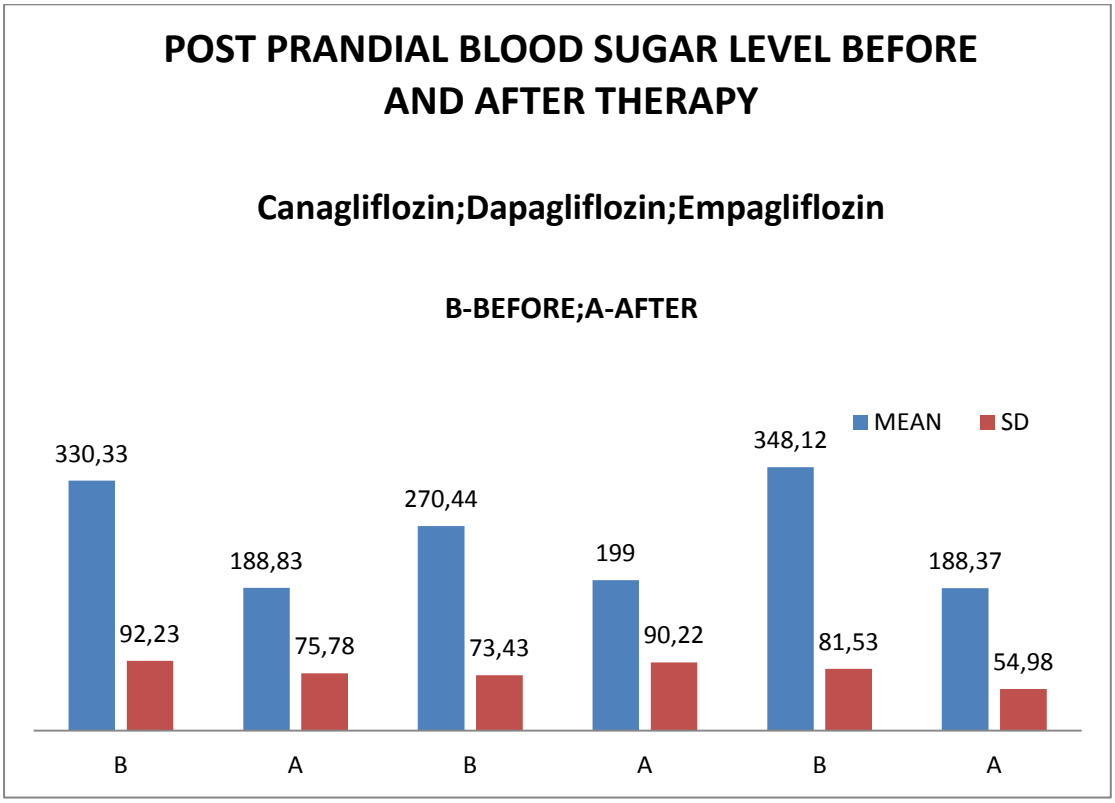


MEAN	80.16	76.08	78.44	74.22	90.12	85
SD	12.77	6.41	8.079	4.841	8.806	7.502

Table 8:POST PRANDIAL BLOOD SUGAR VALUE BEFORE AND AFTER THERAPY

CANAGLIFLOZIN		DAPAGLIFLOZIN		EMPAGLIFLOZIN	
BEFORE mg/dl	AFTER mg/dl	BEFORE mg/dl	AFTER mg/dl	BEFORE mg/dl	AFTER mg/dl
385	209	306	160	448	135
332	136	291	198	437	277
360	146	282	143	336	124
285	176	248	177	304	125
370	271	154	173	324	270
281	126	216	155	191	140
337	390	389	175	165	179
500	128	255	174	380	157
232	200	374	436		
140	140				
424	176				
318	168				





MEAN	330.33	188.83	279.44	199	348.12	188.37
SD	92.23	75.78	73.43	90.22	81.53	54.98

RESULTS

In all 35 subjects were recruited and six were eliminated because of inadequate drug exposure period. Final study subjects number remained at 29 subjects;12 subjects were on canagliflozin,9 on dapagliflozin and 8 on Empagliflozin.

AGE DISTRIBUTION OF THE SUBJECTS:

The mean age of the subjects on canagliflozin is 54.33 ± 9.93years:of the subjects on dapagliflozin 59.77 ± 15.23 and an empagliflozin 50.88±9.92years.The age distribution of the three groups are not statistically significantly different (cana vs dapa p=0.37),(cana vs empa p=0.46),(dapa vs empa p=0.17).

SEX DISTRIBUTION:

The sex distribution in the canagliflozin group are M:F=6:6 ; in the dapagliflozin group are M:F=5:4 ; and in the Empagliflozin group are M:F=2:6.The sex distribution in the three groups are not uniform for the simple reason, subjects are recruited on a first come basis. This also explains the different number of subjects on canagliflozin, dapagliflozin and Empagliflozin.

RESIDENCE:

The study subjects are drawn from around Madurai city and the city proper. The distribution of subjects between urban, rural and semi urban residences were not uniform between the three groups. In the Cangliflozin group 8 subjects were from urban localities,3 from semi urban and 1 from rural locality.

In the dapagliflozin group 7 subjects were from the urban locality,1 each from semi urban and rural localities.

In the Empagliflozin group 6 subjects were from urban localities and 2 from semi urban localities.

BMI:

In the canagliflozin group the BMI value before therapy are 28.18±2.99(M±SD) and after therapy 26.9±3.2.Though it is not statistically significantly different (P=0.32) there is a reduction of 1.28 points in BMI after therapy with canagliflozin.

In the dapagliflozin group the BMI value before therapy is 25.6±3.41 and after therapy is 24.8 ± 2.69.Though these values were not statistically significantly different there is fall of 0.78 points in BMI after therapy with Dapagliflozin.(P=0.19)

In the Empagliflozin group the BMI before therapy is 27.46±2.76 and after therapy is 25.79 ± 2.08.Though these values are not statistically significantly different (P=0.6) there is observed a fall of 1.67 points in the BMI after therapy.

In the Canagliflozin group two subjects showed an increase in BMI after therapy.

In the Dapagliflozin group three subjects did not show any change in BMI and one subjects actually showed increase in BMI.

In the Empagliflozin group three subjects did not show any change in BMI.

The before treatment BMI of the three samples were not statistically significantly different.

The after treatment fall in the mean BMI is marked in the Empagliflozin group (1.67 points),moderate in the Canagliflozin group (1.28 points) and least with the Dapagliflozin group (0.78 points).

BODY WEIGHT:

The body weight of Canagliflozin group before therapy is 74.8±13.02 kgs and after therapy was 71.08±11.01 kgs.The fall in body weight of 3.75kgs was not statistically significant (P=0.51).Two subjects had gained 7kg and 1kg respectively.

The body weight in the Dapagliflozin group in 64.7±9.38 kgs before therapy and 63.04±7.46 kgs after therapy.The mean fall of 1.66 kgs after therapy.Three subjects in this group did not shows any changes in body weight after therapy.Two subjects gained 2kgs each with therapy in this group.

The body weight in the Empagliflozin group before therapy is 69.13±11.58kgs and after therapy 65±11.11kgs.This mean loss of 4.02kgs in this group was not statistically significant (P=0.76).Three subjects in this group did not loose any weight after therapy.

The mean weight between there these samples before therapy is not significantly different.

SYSTOLIC BP:

The systolic blood pressure in the canagliflozin group before therapy is 137.9±22.3 mmhg and after therapy is 129.3±11.2 mmhg.This fall of 8.6 mmhg with therapy was not statistically significantly less (P=0.25).Four subjects in this group had a rise of 9,6,8 and 2mmhg with therapy. One subject systolic BP did not change with therapy.

In the Dapagliflozin the systolic BP before therapy is 144.1±27.46 mmhg and after therapy 134.4±26.8 mmhg.This fall of a mean 9.7 mmhg is statistically low (P=0.02).Only one subjects in the group had a risk of 27mmhg systolic BP after therapy.

In the Empagliflozin group the systolic BP before therapy is 155.3±12.4 mmhg and after therapy 140±9.7mmhg.This fall of 14.4mmhg is not statistically significantly low. Only one subjects in this group did not show any changes in the systolic BP.

The systolic BP in the Empagliflozin group was statistically different before the start of therapy. It was high compared to Canagliflozin (P=0.04) and Dapagliflozin (P=0.0001) groups. The statistical difference is maintained only between Canagliflozin and Empagliflozin group after therapy.

DIASTOLIC BP:

The diastolic BP in the Canagliflozin before therapy is 80.2±12.8mmhg and after therapy 76.1±6.4mmhg. This 4.1 mmhg fall in diastolic pressure in this group is statistically significant had a risc of diastolic BP after therapy at 11,9,2 and 10mmhg respectively.

The diastolic BP in the Dapagliflozin group before therapy is 78.4±8.1mmhg and after therapy 74.2±4.8mmhg.This 4.2 mmhg mean fall of diastolic BP was not significantly low (P=0.23).Two subjects in this group showed 2 and 11 mmhg elevation of diastolic BP and two other subjects should no change in their diastolic BP after therapy.

In the Empagliflozin group the diastolic BP before therapy is 90.1±8.8mmhg and after therapy 85±7.5mmhg.This 5.1 mmhg fall of diastolic pressure is not statistically low (P=0.2).One subject in this group did not show

any change in the diastolic BP after therapy and one subject showed a risc of 14mmhg after therapy.

Before the start of therapy Empagliflozin group had a statistically high blood pressure compared to the Dapagliflozin group(P=0.01) and Canagliflozin group (P=0.05).That statistical difference was maintained post therapy with Dapagliflozin group (P=0.01) and Empagliflozin group (P=0.02).

2 Hours post prandial blood sugar:

Two hour post prandial sugar value in the Canagliflozin group before therapy are 330.3±92.2mgm/dl and after therapy 188.8±75.8 mgm/dl.This fall of 141.5mgm/dl of blood sugar is statistically highly significant (P<0.001).Only one subject in this group had a 53 mgm/dl risc in post prandial blood sugar value and one other subjects did not shows any difference in the 2 hour post prandial blood sugar.

Two hour post prandial blood sugar value in the Dapagliflozin group before therapy is 279.4±73±4 mgm/dl and after therapy 199±90.2 mgm/dl.This mean fall of 80.4 mgm/dl of 2 hour post prandial blood sugar value is statistically significantly low (P=0.05).Only one subject in this group had a risc of 62mgm/dl of 2 hour post prandial blood sugar value after therapy.

Two hour post prandial blood sugar values before therapy in the Empagliflozin group is 348.1 ± 188.4 mgm/dl and after therapy 188.4±55mgm/dl.This 159.7mgm/dl fall in ppbs of this group is statistically highly significant (P<0.001).No subject in this group showed an elevation of blood sugar values after therapy.

The 2 hours post prandial blood pressure values in all the three groups before therapy are not statistically different.

DISCUSSION

SGLT2 inhibitors are a new class of anti diabetics which act independently of insulin secretion and insulin sensitization. They address a compensatory renal mechanism and help diabetic subjects achieve better diabetic control. They block the renal tubular glucose reabsorbtion mechanisms involving the SGLT mechanism. In every diabetic as a compensatory mechanism the system gets induced and almost completely reabsorbs the excess glucose that is filtered by the glomerulus. The only apprehension when such a manipulation was contemplated is the interference with glucose absorption elsewhere like in the gut and the consequence of excess glucose in the urine that comes in constant with the genito urinary tracts of men and women. Such apprehensions are dispelled by the highly selective nature of the present derivatives of phlorizin which act almost exclusively on the SGLT2 paths. In real life UTI and genital infections are not very common with SGLT2 inhibitors usage as they drastically reduce the tissue glucose levels which also contribute to such fungal infections.

The loss of approximately 70gms of glucose in subjects taking SGLT2 inhibitors, which amounts to some degree of starvation and excess excretion of water and sodium with the forced glycosuria were expected to result in at least symptomatic side effects. Unlike the presence of sugar in the urine which is unequivocally harmful to the patients, polyurea, water and salt depletion and some degree of starvation had both positive and negative results. Some patients do complains of polyurea and polydipsia. Many have postual hypotension and reduction in systolic and diastolic blood pressure. Some of the cardiovascular benefits which were demonstrated in Empa -Reg trial utilizing Empagliflozin might be the result of partial starvation.

With the availability of three agents in the same class of drugs, commercial interests more than scientific benefits prevail. In our small, pilot, observational study we have weakly attempted to have a head to head comparision between the three commercially available agents.

For such an observation study we have selected a well attended diabetic clinic situated in the heart of Madurai city to collect patients.

Results revealed than the 2 hour post prandial blood sugar value showed a significant fall in all the three group of patients.

(Canagliflozin=141.5,Dapagliflozin=80.4,Empaliflozin=159.7).Thus in their hypoglycemic effect Empagliflozin seems the best.

The changes in the BP post therapy are (Canagliflozin=8.6/4.1mmhg,Dapagliflozin=9.7/4.2mmhg,Empagliflozin=14.4/ 5.1mmhg). Though only the systolic BP values in the Dapagliflozin group reached statistical significance, BP responses could be called equal. The greater fall in the Empagliflozin group is probably due to the higher levels that prevailed before therapy.

The fall in the body weight are(Canagliflozin=3.75kgs,Dapagliflozin=1.66kgsandEmpagliflozin=4.02kgs).Though none of the groups reached significance, the weight loss is observable.

The changes in the BMI points are (Canagliflozin=1.28,Dapagliflozin=0.78, and Empagliflozin=1.67)

Thus the best results are observable with Empagliflozin on the blood sugar, blood pressure and body weight parameters.

CONCLUSION

This study has limitations because of the small number, being only observational and pilot study. Only the age group of the subjects and body weight were in the same range in the three groups. However the following conclusions can be made from the observed data.

1.Body weight and BMI fell in all the three groups with Canagliflozin 100mg/day, Dapagliflozin 10mg/day, and Empagliflozin 25mg/day. The best fall has observed with Empagliflozin

2.Fall in the systolic and diastolic blood pressure did not reach significance in all the three groups. The Empagliflozin group which had high levels to start with should greater fall.

3.The blood sugar reductions at 2 hour post prandial blood sugar value were statistically significance in all the three groups. The higher reductions are seen with the Empagliflozin group.

4.Thus it can be considered that Empagliflozin among the 3 available SGLT2 inhibitor at maximum permitted doses appears slightly more efficacious however the differences were not statistically efficient.

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CASE RECORD FORM

1.**Personal details:**

Name of the patient: ..... **Date:** .....

MR Number ..... **Age .**..... **Sex:** Male/Female

Occupation:

Address: .....

.....

.....

2.**Medical history:**

Type 2 DM	: Yes/No	Duration of DM	:
HTN	: Yes/No	Duration of HTN	:
Family history of DM	: Yes/No	Family history of HTN	:Yes/No
Smoking	: Yes/No	Alcoholic	:Yes/No

3.**Laboratory investigation**:

Parameters			**Baseline**	**Visit 1 (8 week)**	**Visit 2 (16 week)**
Microalbuminuria					
Blood pressure					
FMD	**Before inflating**	**Systole**			
		Diastole			
	After inflating	**Systole**			
		Diastole			

4.**Treatment:**

Therapy	**Drug Name**	**Duration**
Study drug		
Oral hypoglycemic		
Anti hypertensive drug		
Others		

5.**Side effects:**

6.**Any other details:** .....

.....

Doctor's signature: .....

ERRATA

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