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Review Article

Diabetes and its Complications and SGLT-2 Inhibitors: A Novel Therapy for Type 2 Diabetes Mellitus

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ABSTRACT

The incidence of type 2 diabetes mellitus is increasing worldwide. The pharmacotherapy for type 2 diabetes until the last decade only consisted of biguanides, sulphonylureas, and insulin. The existing therapeutic classes of antidiabetic drugs are not adequately effective in maintaining long-term glycemic control in most patients, even when used in combination. One emerging novel therapeutic class of antidiabetic drugs is sodium glucose cotransporter 2 (SGLT2) inhibitors. SGLT2 accounts for 90% of the glucose reabsorption in the kidney. The SGLT2 inhibitors increase urinary excretion of glucose and lower plasma glucose levels in an insulin-independent manner. Forxiga (Dapagliflozin) the most prominent molecule in this class is currently approved by USFDA. Other members of this class (eg, sergliflozin, remogliflozin) are also effective. This class of novel agents can effectively control blood sugar level without producing weight gain or hypoglycemia.

Keywords: SGLT2 inhibitors, dapagliflozin, sergliflozin, canagliflozin, remogliflozin, new antidiabetic drug

INTRODUCTION

Diabetes mellitus is a metabolic disorder of multiple etiologies characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or a combination of both. According to estimates from the International Diabetes Federation, the global incidence of diabetes mellitus in 2010 was ~6.6% and it was predicted to increase to ~7.8% by 2030, representing an increase of 153 million patients.[1] It is the most common non-communicable disease worldwide and the fourth to fifth leading cause of death in developed countries.[2] Diabetes also contributes to 5% of the total mortality.[3]

Type 2 diabetes has become a major health concern all over in Asia. Developing countries such as India have had the maximum increases in the last few years. The current prevalence of type 2 diabetes is 2.4% in the rural population and 11% in the urban population of India. It has been estimated that by the year 2025, India will have the largest number of diabetic subjects in the world.[4]

Diabetes mellitus is a heterogeneous group of disorders characterized by high blood glucose levels.[5] Several distinct forms of diabetes exist which are caused by a complex interaction of genetics, environmental factors and life-style choices. Some forms are characterized by absolute insulin deficiency or a genetic defect leading to defective insulin secretion while other forms share insulin resistance as their underlying etiology.

The greatest increase in prevalence is expected to occur in Asia and Africa. The increase in incidence of diabetes in developing countries follows the trend of urbanization and lifestyle

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changes.[6] Many causes have been postulated for the rise in the number of cases, including urbanization, sedentary lifestyles, poor nutrition & obesity.[7]

The metabolic abnormality can be improved by various means to ameliorate the deficiency of insulin effects. There are characteristics symptoms of diabetes such as polydipsia, polyuria and weight loss often occur. In severe cases, ketoacidosis or hyperglycemic hyperosmolar states may occur and lead to disturbances of consciousness, coma and even death unless treated appropriately.

Diabetes is a metabolic disorder, with long duration of diabetic metabolism, diabetes specific complications, chiefly involving small vessels (retinopathy, nephropathy and neuropathy), may ensure and lead to serious outcomes such as visual disturbance, renal failure and gangrene. Diabetes accelerates and exacerbates the occurrence of arteriosclerosis, increasing the risks for myocardial infarction, cerebral infraction and occlusive artery disease of the lower extremities. These complications constitute the major causes of morbidity and mortality in diabetic patients. So, diabetes is one of the most debilitating common illnesses and requires lifelong management.[8]

Type 2 diabetes mellitus is a complex trait because both genetic and environment factors play a role in the disease etiology. Type 2 diabetes mellitus is the most common form of diabetes, accounting for > 90% of all cases in the developed world.[9]

The etiology of type 2 diabetes mellitus is intricate and multifaceted, but virtually all patients contend with both relative insulin deficiency and insulin resistance to varying degrees. People with type 2 diabetes are not dependent on exogenous insulin, but may require it for the control of blood glucose levels if this is not achieved with diet alone or with oral hypoglycemic agents. The resulting hyperglycemia can facilitate ß-cell failure in the pancreas and worsen insulin resistance, thus triggering a cycle of impaired metabolism and glucotoxicity.[10] High caloric intake and physical inactivity are major contributors to obesity which within the appropriate genetic background, can cause insulin resistance, hyperglycemia & glucotoxicity mediated by pancreatic ß-cell failure. Hyperglycemia contributes to and exacerbates insulin deficiency by increasing apoptosis of ß-cells and diminishing ß-cell mass, thus reducing gene transcription, synthesis and secretion of insulin.[11]

It is now well established that hyperglycemia and glucotoxicity contribute to disease progression in patients with type 2 DM and therefore, hyperglycemia is a risk factor for the development of long-term complications, including microvascular disease as well as macrovascular disease.[12]

THE CURRENT SCENARIO OF DIABETES IN INDIA

India, the world's second most populous country, now has more people with type 2 DM (more than 50 million) than any other nation. With India having the highest number of diabetic patients in the world, the sugar disease is posing an enormous health problem in the country. Calling India, the diabetes capital of the world. According to a WHO fact sheet on diabetes, 2004 recorded an estimated 3.4 million deaths due to consequences of high blood sugar. WHO also estimates that 80 % of diabetes deaths occur in low and middle-income countries & projects that such deaths will double between 2005 and 2030.

A glance at statistics from Global Data proves one point: that the two countries having the highest diabetes prevalence (India and China) score quite low when it comes to the expenditure on disease.

Diabetes also imposes large economic burdens in the form of lost productivity and foregone

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economic growth. It has been estimated that the global burden of type 2 diabetes mellitus for 2010 would be 285 million people (2010) which is projected to increase to 438 million in 2030; a 65 % increase Similarly, for India this increase is estimated to be 58%, from 51 million people in 2010 to 87 million in 2030.

The impacts of type 2 DM are considerable: as a lifelong disease, it increases morbidity and mortality and decreases the quality of life. At the same time, the disease and its complications cause a heavy economic burden for diabetic patients themselves, their families and society. A better understanding about the cause of a predisposition of Indians to get type 2 DM is necessary for future planning of healthcare, policy and delivery in order to ensure that the burdens of disease are addressed.[13]

Insulin resistance and type 2 diabetes mellitus

Insulin resistance is a characteristic feature of most patients with type 2 diabetes mellitus and is almost a universal finding in type 2 diabetic obese patients. In obese subjects, insulin levels typically increase to maintain normal glucose tolerance. Basal and total 24-h rates of insulin secretion are three to four times higher in obese insulin-resistant subjects than in lean controls.[14] The hyperinsulinemia associated with insulin resistance results from a combination of an increase in insulin secretion and a reduction in insulin clearance rates.

The insulin resistance of obesity and type 2-diabetes is characterized by defects at many levels with decreases in receptor concentration and kinase activity, the concentration and phosphorylation of IRS-1 and IRS-2, PI-3-K activity, glucose transporters translocation and the activity of intracellular enzyme.[15] Insulin increases glucose transport in fat and muscle cells by stimulating the translocation of the transporter GLUT4 from intracellular sites to the plasma membrane. GLUT4 is found in vesicles that continuously cycle from intracellular stores to the plasma membrane. Insulin increases glucose transport by increasing the rate of GLUT4 vesicle exocytosis and by slightly decreasing the rate of internalization.[16]

Insulin causes remodeling of cortical actin filaments just below the plasma membrane and induces membrane ruffling. The docking and fusion of the GLUT4 vesicle at the plasma membrane may also be subject to regulation by insulin. Circulating free fatty acids (FFAs) derived from adipocytes are elevated in many insulin-resistant states and have been suggested to contribute to the insulin resistance of diabetes and obesity by inhibiting glucose uptake, glycogen synthesis and glucose oxidation and by increasing hepatic glucose output. Elevated FFAs are also associated with a reduction in insulin-stimulated IRS-1 phosphorylation and IRS-1-associated PI-3-K activity. The link between increased circulating FFAs and insulin resistance might involve accumulation of triglycerides and fatty acid-derived metabolites (diacylglycerol, fatty acyl-CoA and ceramides) in muscle and liver.

In addition to its role as a storage depot for lipid, the fat cell produces and secretes a number of hormones, collectively called adipokines, which may profoundly influence metabolism and energy expenditure. Expression of tumor necrosis factor a (TNF-a) is increased in the fat of obese rodents and humans and has been shown to produce serine phosphorylation of IRS-1, resulting in reduced insulin receptor kinase activity and insulin resistance.[17]

ß- Cell dysfunction in type 2 diabetes mellitus

In type 2 diabetes, more moderate abnormalities of secretion that cause glucose intolerance are present only if insulin resistance is also present. The genetic basis of ß-cell dysfunction in this form of diabetes is more complex involving both multiple interacting genes and environmental factors which determine whether diabetes will develop and at

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what age. Despite a genetic predisposition, diabetes may never manifest and hyperglycemia, when it occurs usually does so later in life (after 50 years of age).The compensatory hypersecretion of insulin in insulin-resistant states is due to an expansion of ß-cell mass and alteration in the expression of key enzymes of ß-cell glucose metabolism and is believed to be a consequence of increased levels of this glycolytic enzyme hexokinase. In normal pancreatic ß-cells, glucokinase mediates the conversion of glucose to glucose 6-phosphate and determines the threshold at which glucose stimulates insulin secretion.[18]

Insulin resistance is associated with increased ß-cell hexokinase activity, leading to secretion of insulin at lower glucose concentration. It has been suggested that increased free fatty acids in serum could precipitate ß-cell failure. Short-term exposure of pancreatic islets to free fatty acids increases insulin secretion but long-term exposure inhibits glucose-induced insulin secretion and biosynthesis and may lead to ß-cell deaths by apoptosis. These effects may be mediated by increased expressions of proteins which uncouple glucose metabolism from oxidative phosphorylation, a key link between ß-cell glucose metabolism and insulin secretion.[19]

Genetic aspect of type 2 diabetes mellitus

Diabetic islets show reduced insulin gene transcription. This might be due to at least in part, to reduced insulin action in that tissue and indicate that activation of insulin gene transcription is an important effect of insulin-mediated signaling. Genetic variation in the gene encoding Calpain-10, a ubiquitously expressed cysteine protease, has also been associated with type 2 diabetes, increasing risk as much as three-fold through affects on both the normal function of the ß-cell and insulin action in muscle and fat.[20]

Current diagnostic criteria of diabetes mellitus

Many persons with type 2 diabetes already show the presence of the long-term complications associated with diabetes at the time of diagnosis. It is now widely accepted that if diabetes is detected early and adequate steps are taken, it may be possible to significantly delay the onset and progression of these complications. When a patient is symptomatic and fasting plasma glucose (FPG) is unequivocally elevated, diagnosis of diabetes does not present any difficulty. When a patient is without clinical symptoms diagnosis of diabetes is more difficult. Revised criteria for diagnosing DM have been issued by a consensus panel of experts from the National Diabetes Data Group and the WHO. The revised criteria reflect new epidemiological and metabolic evidence and are based on the following premises:

1. The spectrum of fasting plasma glucose (FPG) & the response to an oral glucose load varies in normal individuals.
2. Diabetes mellitus defined as the level of glycemia at which diabetes-specific complications are noted and not on the level of glucose tolerance from a population-based viewpoint.

Glucose tolerance is classified into three categories based on the fasting plasma glucose:

1. FPG <5.56 mmol/ l (<100 mg/dl) is considered normal,
2. FPG >5.56 mmol/l (>100 mg/dl) but <7.0 mmol/l (<126 mg/dl) is defined as impaired fasting glucose (IFG) and
3. FPG >7.0 mmol/l (>126 mg/dl) warrants the diagnosis of diabetes mellitus.

IFG is a new diagnostic category defined by the expert committee on the diagnosis and classification of diabetes mellitus (American Diabetes Association). It is analogous to IGT, which is defined as plasma glucose levels between 7.8 and 11.1 mmol/l (140 and 200 mg/dl) 2 hrs after a 75- gram oral glucose load.

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Individuals with IFG or IGT are at substantial risk for developing type 2 diabetes mellitus and cardiovascular disease in the future, though they may not meet the criteria for diabetes mellitus. Thus the criteria for diagnosis of diabetes mellitus are as follows:

• Symptoms of diabetes plus random blood glucose concentrations >11.1 mmol/l (>200 mg/dl).

• Fasting plasma glucose >7.0 mmol/l (>126 mg/dl) OR

• Two-hour plasma glucose >11.1 mmol/l (>200 mg/dl) during an oral glucose tolerance test. The revised criteria for the diagnosis of DM emphasize FPG as the most reliable and convenient test for diagnosing DM in asymptomatic individuals.

Oral glucose tolerance testing although still a valid mechanism for diagnosis of DM is not recommended as part of routine screening. Some investigators have advocated acetylated hemoglobin (HbA1c) as a diagnostic test for DM. Though there is strong correlation between elevations in plasma glucose and HbA1c, the relationship between FPG and HbA1c in individuals with normal glucose tolerance or mild glucose intolerance is less clear and the test is not universally standardized or available.[21]

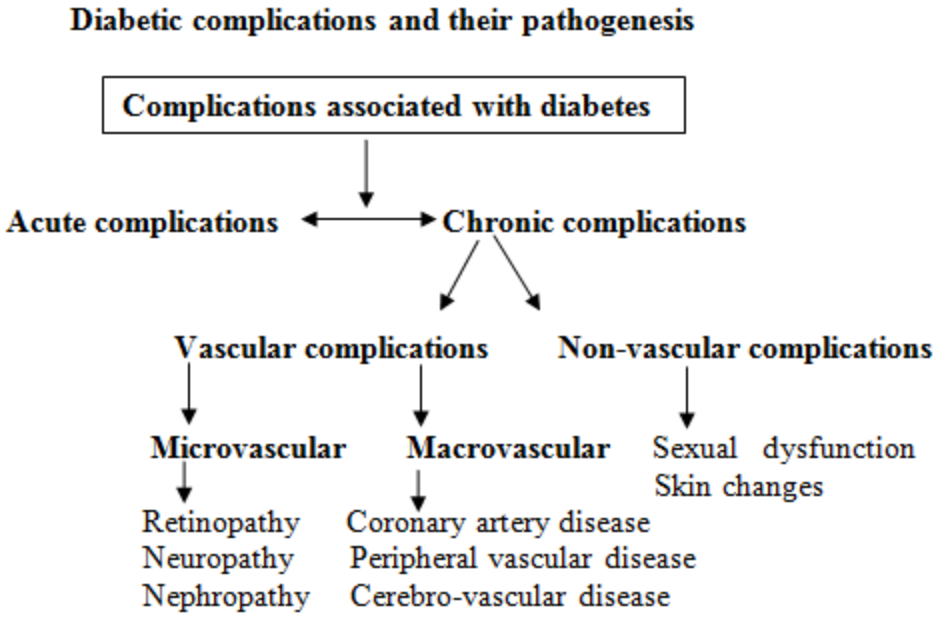

Fig: 1 complications associated with diabetes

a) Acute complications

These include diabetic ketoacidoses (DKA) and non-ketotic hyper-osmolar state (NKHS). While the first is seen primarily in individuals with type 1 DM, the latter is prevalent in individuals with type 2 DM. Both disorders are associated with absolute or relative insulin deficiency, volume depletion and altered mental state. In DKA, insulin deficiency is combined with counter-regulatory hormone excess (glucagon, catecholamines, cortisol & growth hormone). The decreased ratio of insulin to glucagon promotes gluconeogenesis, glycogenolysis and ketone body formation in the liver and also increases free fatty acid and amino-acid delivery from fat and muscle to the liver. Ketosis results from a marked increase in free fatty acid release from adipocytes due to increased lipolysis. In DKA, nausea and vomiting are often present. Lethargy and CNS depression

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may evolve into coma in severe DKA. Cerebral edema, an extremely serious complication, is seen most frequently in children.

NKHS is most commonly seen in elderly individuals with type 2 DM. Its most prominent features include polyuria, orthostatic hypotension and a variety of neurological symptoms including altered mental state, lethargy, obtundation, seizure and possibly coma. Insulin deficiency and inadequate fluid intake are the underlying causes of NKHS. Insulin deficiency leads to hyperglycemia, which induces an osmotic diuresis leading to profound intravascular volume depletion.

b) Chronic complications

The chronic complications of diabetes mellitus affect many organ systems and are responsible for the majority of morbidity and mortality. Chronic complications can be divided into vascular and nonvascular complications. The vascular complications are further subdivided into microvascular (retinopathy, neuropathy, and nephropathy) and macrovascular complications (coronary artery disease, peripheral vascular disease and cerebrovascular disease). Nonvascular complications include problems such as gastroporesis, sexual dysfunction and skin changes. As a consequence of its chronic complications, DM is the most common cause of adult blindness, a variety of debilitating neuropathies, cardiac and cerebral disorders. Treating the complications of diabetes costs more than controlling the disease.

Early in the course of diabetes, intracellular hyperglycemia causes abnormalities in blood flow and increased vascular permeability. This reflects decreased activity of vasodilators such as nitric oxide, increased activity of vasoconstrictors such as angiotensin II and endothelin-1 and elaboration of permeability factors such as vascular endothelial growth factor (VEGF). In diabetic arteries, endothelial dysfunction seems to involve both insulin resistance specific to the phosphotidylinositol-3-OH kinase pathway and hyperglycemia.

I. Diabetic retinopathy

Diabetic retinopathy occurs in 3/4 of all persons having diabetes for more than 15 years and is the most common cause of blindness. There is appearance of retinal vascular lesions of increasing severity, culminating in the growth of new vessels.

Diabetic retinopathy is classified into two stages: non-proliferative and proliferative. The non-proliferative stage appears late in the first decade or early in the second decade of disease and is marked by retinal vascular microneurisms, blot hemorrhages and cotton-wool spots and includes loss of retinal pericytes, increased retinal vascular permeability, alterations in regional blood flow and abnormal retinal microvasculature, all of which lead to retinal ischemia.

In proliferative retinopathy there is the appearance of neovascularization in response to retinal hypoxia. The newly formed vessels may appear at the optic nerve and/or macula and rupture easily, leading to vitreous hemorrhage, fibrosis and ultimately retinal detachment.[22]

II. Neuropathy

About half of all people with diabetes have some degree of neuropathy, which can be polyneuropathy, mono-neuropathy and/or autonomic neuropathy. In polyneuropathy there is loss of peripheral sensation which, when coupled with impaired microvascular and macrovascular junction in the periphery can contribute to non-healing ulcers, the leading cause of non-traumatic amputation.

There is thickening of axons, decrease in microfilaments and capillary narrowing involving small myelinated or non-myelinated C-fibers. It can occur both from direct hyperglycemia-induced damage to the nerve parenchyma and from neuronal ischemia

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leading to abnormalities of microvessels such as endothelial cell activation, pericyte degeneration, basement membrane thickening and monocyte adhesion. Mono-neuropathy is less common than polyneuropathy and includes dysfunction of isolated cranial or peripheral nerves. Autonomic neuropathy can involve multiple systems, including cardiovascular, gastrointestinal, genitourinary, sudomotor and metabolic systems.[23]

III. Nephropathy

This is a major cause of end-stage renal disease. There are glomerular hemodynamic abnormalities resulting in glomerular hyperfiltration leading to glomerular damage as evidenced by microalbuminurea. There is overt proteinuria, decreased glomerular filtration rate and end-stage renal failure. Dysfunction of the glomerular filtration apparatus is manifested by microalbuminurea and is attributed to changes in synthesis and catabolism of various glomerular basement membrane macromolecules such as collagen and proteoglycans, leading to an increase in glomerular basement thickening. Another possible mechanism to explain the increase in permeability of the glomerulus is the increase in renal VEGF levels observed in preclinical models of diabetes, since VEGF is both an angiogenic and a permeability factor.[24]

IV. Hypertension

Hypertension can accelerate other complications of diabetes mellitus, particularly cardiovascular disease and nephropathy. Antihypertensive agents should be selected based on the advantages and disadvantages of the drugs in the context of the individual patient's risk-factor profile. DM-related considerations include the following:

α-adrenergic blockers slightly improve insulin resistance and positively impact the lipid profile. α-blockers and thiazide diuretics can increase insulin resistance, negatively impact the lipid profile and slightly increase the risk of developing type 2 diabetes. ß-blockers, because of the potential masking of hypoglycemic symptoms, are effective agents and hypoglycemic events are rare when cardio-selective ß1 agents are used.

Central adrenergic antagonist's and vasodilators are lipid and glucose neutral. Sympathetic inhibitors and α-adrenergic blockers may be associated with orthostatic hypotension in the diabetic individual with autonomic neuropathy. Calcium-channel blockers are glucose and lipid. Neutral and may reduce cardiovascular morbidity and mortality in type 2 DM, particularly in elderly patients with systolic hypertension.

V. Infections

Individuals with diabetes mellitus exhibit a greater frequency and severity of infection. The reasons for this include incompletely defined abnormalities in cell-mediated immunity and phagocyte function associated with hyperglycemia as well as diminished vascularization secondary to long-standing diabetes.

Many common infections are more frequent and severe in the diabetic population, whereas several rare infections are seen almost exclusively in the diabetic population (e.g. rhinocerebral mucormycosis and malignant otitis externa which is usually secondary to *P. aeruginosa* infection in the soft tissue surrounding the external auditory canal). Pneumonia, urinary tract infection and skin and soft tissue infections are all more common in the DM population. Gram-negative organisms, e.g. *S. aureus* and *Mycobacterium tuberculosis*, are more frequent pathogens in patients of DM. Diabetic patients have an increased rate of colonization of *S. aureus* in skin folds and nares and also have a greater risk of postoperative wound infections.[25]

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MECHANISMS OF HYPERGLYCEMIA-INDUCED DAMAGE

Many hypotheses about how hyperglycemia causes diabetic complications have generated a large amount of data as well as several clinical trials based on specific inhibitors of these mechanisms. The main hypotheses are: the Aldose Reductase theory, Advanced Glycation End Product (AGE) theory, Activation of Protein Kinase C (PKC) isoform theory, Increased Hexosamine Pathway Flux theory and the Reactive Oxygen Intermediate theory.

I. Aldose reductase

This is the first enzyme in the polyol pathway. It is a cytosolic, monomeric oxido-reductase that catalyses the NADPH-dependent reduction of a wide variety of carbonyl compounds, including glucose. Increased intracellular glucose in a hyperglycemic environment results in its increased enzymatic conversion to the polyalcohol sorbitol with concomitant decreases in NADPH. In the polyol pathway, sorbitol is oxidized to fructose by the enzyme sorbitol dehydrogenase with NAD^+ reduced to NADH. Cataract formation in diabetes and galactosemia result from accumulation in the lens of excessive sorbitol synthesized by the action of aldose reductase on glucose or galactose, respectively.

A number of mechanisms have been proposed to explain the potential detrimental effects of hyperglycemia-induced increases in polyol pathway flux. These include sorbitol-induced osmotic stress, decreased (Na^+ + K^+) ATPase activity, an increase in cytosolic NADH/NAD^+ and a decrease in cytosolic NADPH.

Hyperglycemia-induced activation of PKC increases cytosolic phospholipase A2 activity, which increases the production of two inhibitors of Na^+ K^+ ATPase, Arachidonate and PGE2. It has also been proposed that reduction of glucose to sorbitol by NADPH consumes NADPH. As NADPH is required for regenerating reduced glutathione (GSH), this could induce or exacerbate intracellular oxidative stress.[26]

II. Advanced glycation end products

AGEs are found in increased amounts in diabetic retinal vessels and renal glomeruli. AGE inhibitors partially prevented various functional and structural manifestations of diabetic microvascular diseases in retina, kidney and nerve.

The AGE inhibitor amino guanidine lowered total urinary protein and slowed progression of neuropathy. Production of intracellular AGE precursors damages target cells by three general mechanisms: intracellular proteins modified by AGEs have altered function; extracellular matrix components modified by AGE precursors interact abnormally with other matrix components and with the receptors for matrix proteins (integrins) on cells; and plasma proteins modified by AGE precursors bind to receptors of AGE (RAGE) on endothelial cells, mesangial cells and macrophages, inducing receptor-mediated production of reactive oxygen species.

The AGE receptor ligation activates the pleiotropic transcription factors, causing pathological changes in gene expression along with other cellular signaling events, such as activation of mitogen-activated protein (MAP) kinase or PKC, which can lead to cellular dysfunction.[27]

III. Diacylglycerol (DAG) and Protein Kinase C (PKC)

These are critical intracellular signaling molecules that can regulate many vascular functions, including permeability, vasodilator release, endothelial activation and growth factor signaling. The PKC family comprises at least eleven isoform, nine of which are activated by the lipid second messenger DAG. Intracellular hyperglycemia increases the amount of DAG in cultured microvascular cells and in the retina and renal glomeruli of diabetic

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animals. Increased *de novo* synthesis of DAG leads to the activation of PKC- b isoforms which have been shown to mediate retinal and renal blood flow abnormalities. Activation of PKC by raised glucose also induces expression of the permeability-enhancing factor VEGF in smooth muscle cells. Treatment with an inhibitor specific for PKC-B significantly reduced PKC activity in the retina and renal glomeruli of diabetic animals. Concomitantly, treatment significantly reduced diabetes-induced increases in retinal mean circulation time, normalized increases in glomerular filtration rate and partially corrected urinary albumin excretion.[28]

IV. Hexosamine pathway

Shunting of excess intracellular glucose into the hexosamine pathway might also cause several manifestations of diabetic complications. In this pathway, fructose 6-phosphate is diverted from glycolysis to provide substrates for reactions that require UDP-N-acetylglucosamine such as proteoglycans synthesis and the formation of O-linked glycoproteins. Inhibition of the rate-limiting enzyme in the conversion of glucose to glucosamine-glutamine, fructose-6-phosphate amidotransferase (GFAT), blocks hyperglycemia-induced increases in the transcription of TGF a, TGF b and PAI-1. This pathway has also an important role in hyperglycemia induced and fat-induced insulin resistance.[29]

V. Reactive oxygen intermediate theory

Hyperglycemia can increase oxidative stress through both enzymatic and non-enzymatic processes. Glucose metabolism through the glycolytic pathway and TCA cycle produces reducing equivalents used to drive the synthesis of ATP via oxidative phosphorylation in mitochondria. By products of mitochondrial oxidation include free radicals such as superoxide anion, whose generation increases with increased glucose levels. Glucose oxidation also produces free radicals which damage cellular proteins as well as mitochondrial DNA.

Increased oxidative stress reduces nitric oxide levels, damages cellular proteins and promotes leukocyte adhesion to the endothelium while inhibiting its barrier function. Levels of antioxidants such as GSH, vitamin C and vitamin E have been reported to be decreased in patients with diabetes, while the levels of some markers of oxidative stress e.g. oxidized low-density lipoprotein cholesterol are increased. Thus there can be two approaches to designing treatment for the prevention of hyperglycemia-induced complications. First, the neutralization of specific glucotoxins such as reactive oxygen species or AGEs and second, identifying and normalizing the activity of a common signaling pathway used by glucose and glucotoxins to exert their effects.

MANAGEMENT OF DIABETES MELLITUS

Diabetes can be managed by drug therapy and non-pharmacological therapy. The cornerstone of non-pharmacologic therapy is lifestyle modifications, including nutritional therapy, physical activity and avoidance of smoking. Education of the patient in diabetes self-care, including self-monitoring of blood glucose levels, is also vital. Because uncontrolled hyperglycemia is a risk factor for diabetes complications (neuropathy, retinopathy and nephropathy) as well as cardiovascular disease, the primary goal of therapy for type 2 DM is glycemic control.

The use of current agents for type 2 DM is often limited by their potential to induce significant adverse effects. For instance, Metformin can cause gastrointestinal effects such as diarrhea and nausea and rarely, lactic acidosis, whereas sulfonylureas or insulin can induce hypoglycaemia as well as weight gain. Thiozolidinedione use is also associated with weight gain. Thiozolidinedione use is also associated with weight gain and edema.[30] Newer drugs such as the incretin mimetics, may

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produce nausea, vomiting and diarrhea. Glycemic control can be difficult to attain, even a combination of multiple oral agents and with insulin added. Thus, the quest to develop therapeutic agents with novel mechanisms of action without these side effects continues.

SGLT-2 INHIBITION–A NOVEL STRATEGY FOR DIABETES TREATMENT

Hyperglycemia plays an important role in the pathogenesis of type 2 diabetes mellitus, *i.e*., glucotoxicity & 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 ß-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 anti-diabetic agents have the potential to improve glycemic control while avoiding hypoglycemia, to correct the glucotoxicity and to promote weight loss.[31]

For centuries, the kidney has been considered primarily an organ of elimination and a regulator of salt and ion balance. Although once thought that the kidney was the structural cause of diabetes which in recent years has been ignored as a regulator of glucose homeostasis, is now recognized as a major player in the field of metabolic regulation carbohydrate. Only 2 organs have this capability; the liver and kidney, the latter is responsible for 20% of total glucose production and 40% of that produced by gluconeogenesis. Today we have a better understanding of the physiology of renal glucose transport via specific transporters such as type 2 sodium-glucose cotrasporter (SGLT2). Therefore, the development of novel medications, which effectively lower the plasma glucose level, produce durability of glycemic control and are not associated with hypoglycemia and weight gain, is needed for the management of Type 2 DM patients. Most recently, inhibitors of the renal sodium glucose cotransporter have been developed to produce glucosuria and reduce the plasma glucose concentration.[32]

Glucose transport across cell membranes

Glucose is an essential fuel source for cellular metabolism. The glucose molecule is highly polar and does not cross the lipid bilayer that comprises the plasma membrane of all living cells. Because of this, membrane proteins that facilitate glucose transport from the extracellular to the intracellular space are pivotal for glucose movement across cell membranes. Two distinct classes of glucose transporters exist in the human body.

1) Facilitative glucose transporters (GLUT), a family of proteins that passively facilitate glucose movement from the extracellular to the intracellular space along its chemical gradient and thus, do not consume energy.

2) Sodium-glucose co-transporters (SGLT), a family of proteins that actively transport glucose across cell membranes against its concentration gradient, there by requiring energy source for their action.[33 & 34]

At least 14 different GLUT and seven SGLT have been identified. SGLT couple glucose with sodium transport into the cell. Because sodium is transported along its electrochemical gradient, it provides the energy required for SGLT to transport glucose against its concentration gradient into the cell. SGLT mediate glucose transport across the intestinal lumen and across the epithelial cell in the proximal renal tubule. Both GLUT and SGLT are large-membrane proteins. $GLUT_s$ have 12 trans-membrane domains & more than 12 different types of GLUT have been described. Two different sodium-glucose cotrasporter have

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been described, SGLT1 and SGLT2; both are large-membrane proteins (670 amino acids) and each has 14-transmembrane domains. The homology between SGLT1 and SGLT2 is approximately 58%.[35]

Filtration of glucose by the kidney

The kidney plays a pivotal role in the regulation of the plasma glucose concentration. Approximately 180 liters of plasma with a glucose concentration of approximately 90 mg/dl are filtered by the glomeruli every day.

Filtered plasma in addition to water, salts and amino acids contains approximately 162 g of glucose each day. In normal glucose-tolerant subjects virtually all of this glucose is completely reabsorbed in the proximal tubule. The net result is that no glucose is excreted in the urine. Glucose transport from the lumen across the apical membrane of the epithelial cell occurs against a concentration gradient and therefore requires an active transport process. The early convoluted segment (S1) of the proximal tubule reabsorbs approximately 90% of the filtered renal glucose. This is accomplished by the high-capacity, low-affinity SGLT2 transporter. The remaining 10% of the filtered glucose is reabsorbed by the high-affinity, low-capacity SGLT1 transporter in the distal straight segment (S3) of the proximal tubule.

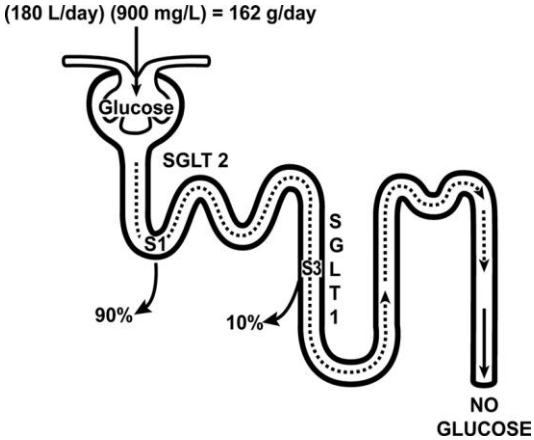

Fig: 2 Renal tubular regulation of glucose reabsorption.

Both SGLT1 and SGLT2 couple glucose transport to the sodium gradient and the sodium electrochemical gradient generated by active sodium transport provides the energy required for glucose transport. After glucose has been transported into the renal proximal tubular cell by the SGLT2 transporter, the sugar exits the basolateral cell border via the GLUT2 transporter. The maximum glucose transport capacity (Tm) of the proximal tubule varies between individuals and on average has a value of approximately 375 mg/min.[36]

Because the filtered glucose load is less than 375 mg/min in non-diabetic subjects, all of the filtered glucose is reabsorbed and returned to the circulation. The amount of filtered glucose is directly related to the plasma glucose concentration. If the filtered glucose load exceeds 375 mg/min, as may occur in T2DM subjects, the Tm is exceeded and all glucose in excess of the Tm is excreted in the urine. The plasma glucose concentration at which the filtered glucose load reaches 375 mg/min is called the threshold. When the threshold is exceeded, the glucose excretion rate increases linearly and parallels the filtered load. The reabsorption and excretion curves display a nonlinear transition as the Tm for glucose is approached.

This “rounding” of the curves is termed splay and it has been explained by heterogeneity in the Tm for individual nephrons and/or glomerulotubular imbalance, *i.e.*, tubular reabsorption is not in balance with the glomerular filtration rate (GFR).

Sodium-glucose co-transporters family

Six different genes that encode for sodium-glucose cotrasporter have been isolated in humans.[41]Only the SGLT1 and SGLT2 have been well characterized in man and their role in gut and kidney glucose transport, respectively, has been well defined.[37]

The SGLT1 gene was first cloned from an intestinal rabbit cDNA library. The human SGLT1

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gene is located at chromosome 22 and spans 72 kb of genomic DNA. It is highly conserved throughout evolution and more than 55 members of SGLT1 have been described in bacteria, yeast, invertebrates and vertebrates. The human SGLT1 gene encodes a 670-amino acid protein, the SGLT1 transporter, which is found in the intestinal mucosa where it transports glucose and galactose from the intestinal lumen across the intestinal mucosa.

SGLT1 is also expressed in the S3 segment of the renal proximal tubule. SGLT1 transports both glucose and galactose with similar affinity for both molecules. It has a glucose/galactose to sodium stoichiometry of 2:1 and possesses a high affinity for both glucose and galactose (Km_0.2mM) but a low transport capacity.[38]

The SGLT2 gene is located at chromosome and it is expressed primarily in kidney cortex. The SGLT2 transporter also is expressed at low levels in the brain and liver. It is the principal glucose transporter in the renal proximal tubule and it is highly selective for glucose over galactose. It has a low affinity for glucose (Km _ 2 mM) with high transport capacity (Tmax_10 nmol/mg protein_min), and it transports one glucose molecule for every sodium ion.[39]
A third SGLT gene has been isolated from a pig renal cell line with a rabbit SGLT1 probe. It has 70% homology to SGLT1 and in expression experiments in oocytes, facilitates amino acid transport into the oocyte.

Thus, it initially was designated as a sodium-amino acid transporter (SAAT1). Subsequent studies have demonstrated that the protein encoded by the SAAT1 gene also facilitates sodium-glucose transport with high selectivity and low affinity to glucose. SGLT2 and SGLT1 actively transport glucose across the proximal convoluted tubule (PCT) cells of the kidney with varying capacities. SGLT2 is a high- capacity, low-affinity transporter found mainly in the s1 segment of the PCT. SGLT2 is thought to account for approximately 90% of reabsorbed glucose and its expression is limited to the kidney. By contrast SGLT1, a low–capacity, high–affinity transporter, is situated in the more distal S2/S3 segment of the PCT and reabsorbs the remaining percentage of the filtered glucose.[40]

Table No. 1 Sodium-glucose co-transporters family.

Transporters	Substrate	Tissue distribution
SGLT1	Glucose and Galactose.	Kidney,Small intestine,Heart & Trachea.
SGLT2	Glucose.	Kidney.
SGLT3	Glucose sensor.	Small intestine ,Thyroid, Testes, Uterus.
SGLT4	Mannose,Glucose, Fructose,Galactose.	Kidney, Small intestine, liver & lung.
SGLT5	Glucose and Galactose.	Kidney.
SGLT6	Myo-inostol, Glucose,& Chiro-inositol	Kidney, Small intestine & Brain.

SGLT2 catalyzes the active transport of glucose against a concentration gradient across the apical (luminal) membrane by coupling it with the transport of sodium, the inward sodium gradient across the luminal epithelium is maintained by ATP- driven active extrusion of sodium across the anti-luminal membrane in to intracellular space which is in equilibrium with

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the blood by basolateral (anti-luminal) glucose transporter type-2 (GLUT2;also known as SLC2A2) and GLUT1(also known as SLC2A1) facilitative glucose transporters.[41]

Sodium-glucose co-trasporter 2 catalyses the active transport of glucose across the luminal membrane by coupling it with the downhill transport of Na^+. The inward Na^+ across the basolateral (anti-luminal) surface in to the intercellular fluid, which is in equilibrium with the blood. Glucose passively diffuses out of the cell down a concentration gradient by basolateral facilitative transporters: glucose transporter type 2 (GLUT2) and GLUT1 Plasma glucose concentrations are normally maintained within a narrow range, which is crucial for organs such as brain, which uses glucose almost exclusively as its energy source.

This balance involves the complex interplay of numerous regulatory processes. Glucose uptake by the central nervous and peripheral tissues is matched by glucose production, which is primarily mediated by the liver and to a lesser degree by the kidney. The filtered load of glucose is the product of the plasma glucose concentration and the glomerular filtration rate. So, as the plasma concentration of glucose increases, the filtered load of glucose increases in a linear manner. When the plasma glucose concentration is greater than ~ 200 mg per 100 ml, all of the filtered glucose is reabsorbed, as the reabsorptive capacity of the $SGLT_s$ not yet saturated.

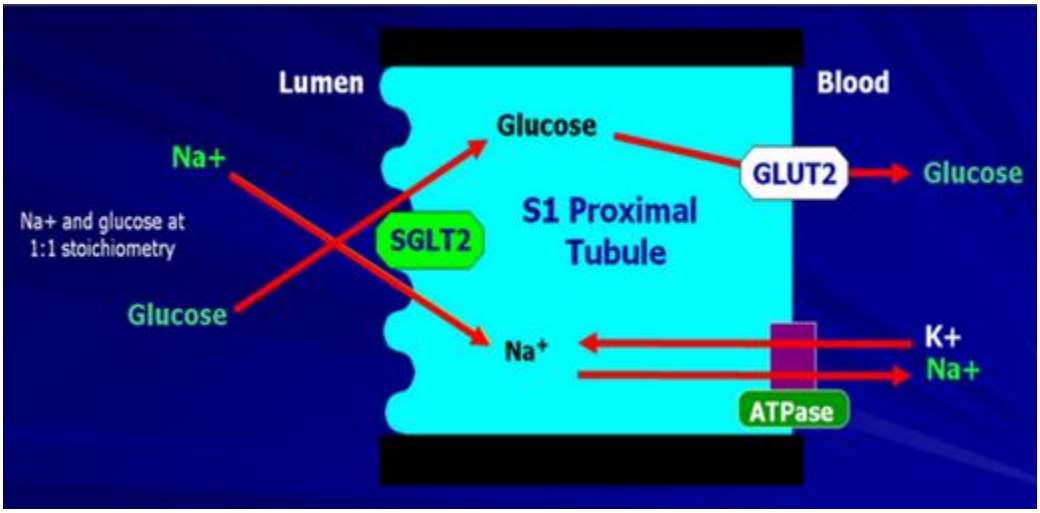

Fig: 3 SGLT2 mediates glucose reabsorption in the kidney.

Two additional sodium-glucose transporters, SGLT4 and SGLT5 have been identified. SGLT4 is a low-affinity transporter for glucose and mannose and the gene is expressed in a variety of tissues including the pancreas. The SGLT5 gene is exclusively expressed in the renal cortex and protein encoded by SGLT5 gene has not been identified, nor has its function been elucidated.

Familial renal glucosuria

Familial renal glucosuria is characterized by urinary glucose excretion in the presence of a normal blood glucose concentration and the absence of other signs of general renal tubular dysfunction.[42] Genetic analysis of families with renal glucosuria has demonstrated that this disorder is caused by mutations in the gene encoding for the SGLT2 transporter and at least 21 different mutations in the SGLT2 gene have

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been described. The majorities of reported SGLT2 mutations are nonsense or frame shift mutations that result in disruption of transmembrane domains, which are essential for sugar binding and sugar transport by the SGLT2 protein. Most of these mutations are inherited in an autosomal recessive mode and the index subject is either homozygous or compound heterozygous. The severity of glucosuria varies markedly among affected individuals, ranging from 20 to 200 g of glucose per 24 h. Of note, affected individuals are asymptomatic and have no history of growth retardation, polyuria, polydipsia, renal disease, or increased urinary tract infection.

Recently, an SGLT2 knockout mouse has been created. Mice lacking the SGLT2 transporter had glucosuria, polyurea and increased food and fluid intake.

However, compared with wild-type animals, the SGLT2 knockout mice had comparable body weight, plasma glucose concentration, GFR and urinary excretion of electrolytes and amino acids. Free-flow micropuncture studies demonstrated a marked decrease in glucose reabsorption in the proximal tubule (6% of the glucose load *vs.* 78% in the wild type). These mutations and the SGLT2 knockout mice collectively emphasize the central role of the SGLT2 transporter in renal glucose reabsorption. They also provide proof of concept that pharmacological inhibition of SGLT2 is a safe and potentially effective strategy for reducing the plasma glucose concentration in diabetic subjects. However, it is important to note that adaptive mechanisms may have developed in prenatal life to compensate for the lack of SGLT2 activity and these mechanisms may not exist during pharmacological inhibition of SGLT2.[43]

Hyperglycemia and renal glucose reabsorption

In Type 1DM and Type 2DM individuals, hyperglycemia results in an increased filtered glucose load. This leads to increased glucose reabsorption via proximal renal tubular cells and as long as the Tm for glucose is not exceeded, no glucose appears in the urine. From a purely theoretical standpoint, hyperglycemia by increasing the interstitial glucose concentration would be expected to attenuate the glucose concentration gradient across the basolateral membrane of the proximal renal epithelial cell and lead to impaired glucose efflux. However, studies in experimental animal models of diabetes consistently have reported an increased rate of glucose reabsorption in the proximal tubule in hyperglycemic diabetic rats during uncontrolled diabetes.

The molecular mechanism responsible for increased renal glucose reabsorption during hyperglycemia involves an increase in the expression of glucose transporter genes in the proximal tubule. Increased SGLT2 gene expression has been reported in renal proximal tubular cells in experimental animals and in humans. Renal tubular cells isolated from the urine of patients with Type 2 DM have an increase in the expression of SGLT2 mRNA and protein and demonstrate an increase in glucose transport. [44]

Several studies also have reported an increase in GLUT2 gene expression in the kidney in models of spontaneous diabetes, *i.e*., the Zucker diabetic rat and in pharmacologically induced (streptozotocin) diabetes.[45] Furthermore, in experimental diabetic animal models, correction of the hyperglycemia with insulin or phlorizin reversed the increase in SGLT2 gene expression caused by hyperglycemia. This has major survival benefits because it allows the kidneys to conserve this critical energy source for the brain, which (with the exception of prolonged fasting) only can metabolize glucose to generate energy for neuronal function. However, in the diabetic patient this adaptive mechanism now becomes

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maladaptive. In the presence of hyperglycemia, it would be desirable for the kidney to excrete the excess filtered glucose load to restore normoglycemia. In contrast, the diabetic kidney has an increased Tm for glucose, thereby minimizing glucosuria and exacerbating the hyperglycemia. When viewed in these terms, it is evident that the kidney contributes to the development and maintenance of hyperglycemia in individuals with diabetes. Based upon these pathophysiological considerations, it follows that development of inhibitors of the renal SGLT2 transporter provides a rational and novel approach to the treatment of diabetic patients. It is important to avoid inhibition of the SGLT1 transporter (which is present in both the gut and kidney), because this would lead to glucose malabsorption and diarrhea.

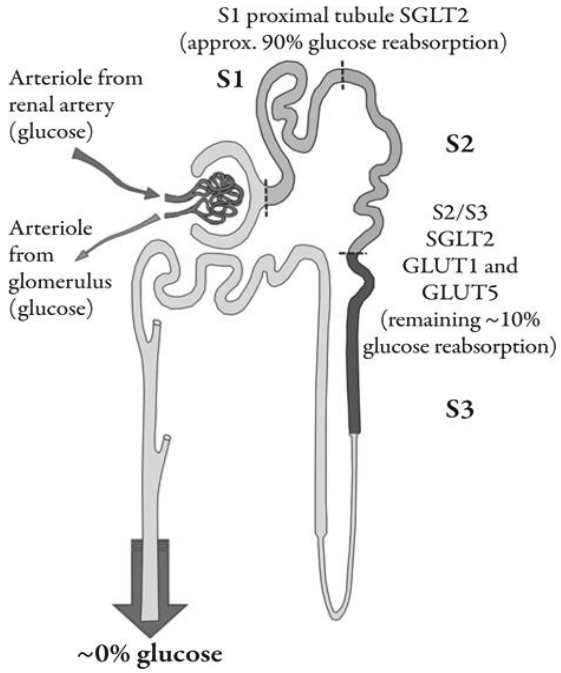

Fig: 4 Renal handling of glucose in a non-diabetic individual.

Virtually all the glucose filtered is reabsorbed, and none appears in the urine. The locations for sodium-glucose co-transporter 2(SGLT2) and SGLT1 are shown. Recent evidence also suggests that the SGLT1 transporter in cells of the proximal small intestine may be responsible for generating the signal leading to the release of incretin hormones in response to nutrient ingestion.[46]

Renal glucose transport in diabetes:

Renal tubular reabsorption is known to undergo adaptations in uncontrolled diabetes; particularly relevant in this context is the up-regulation of renal $GLUT_s$. The increase in extracellular glucose concentration in diabetes lowers its outwardly directed gradient from the tubular cells in to the interstitium. Hence, up-regulation of SGLT2 is an important adaptation in diabetes to maintain renal tubular glucose reabsorption. Uncontrolled diabetes leading to increased expression of SGLT2 has practical significance in that the inhibitors are likely to produce greater degrees of glucosuria in the presence of higher prevailing plasma glucose levels.[47] The kidney has a key role in regulating glucose levels-by mediating the reabsorption of glucose back in to the plasma-following filtration of the blood; this is a crucial evolutionary adaptation to maintaining glucose homeostasis and to retaining calories. This process contribute to the sustained elevated serum glucose levels observed in individuals with diabetes, as they have an increased capacity for renal glucose reabsorption. Inhibition this glucose reabsorption, thereby allowing its excretion in the urine (glycosuria), is therefore emerging as a potential new approach to the treatment of diabetes. Glycosuria, however, has historically been perceived as a sign of metabolic decomposition and of adverse clinical sequelae. Therefore, utilizing this manifestation as a therapeutic strategy for diabetes represents a paradigm shift.

This trasporter is found in a relatively high proportion in a relatively high proportion in the initial segment of the proximal tubule (s1). SGLT2 transports glucose by using the energy

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gradient of sodium reabsorption in the tubular filtration. This process is called secondary active transport and is driven by the electrochemical gradient of sodium in the tubular filtration. As SGLT2 inhibitors do not target the major pathophysiological defects in T2DM- namely insulin resistance and impaired insulin secretion, this class of drug represent a potentially promising new option in the treatment of diabetes. By increasing urinary glucose excretion (UGE), blockage of SGLT2 not only reduces plasma glucose levels to prevent glucotoxicity, but also induces caloric loss, thus promoting body mass reduction and insulin sensitization.[48]

Potential of SGLT inhibition in treating diabetes

The high plasma glucose levels that are characteristics of uncontrolled type 2 DM exceed the maximum threshold of glucose reabsorption, saturating the SGLT receptors and resulting in the increased excretion of glucose in the urine.[49] Patients with type 2 DM also express a significantly higher number of SGLT2 and GLUT2 than healthy individuals, as shown by a preclinical study of cultured PCT cells taken from human patients. Renal glucose uptake is also greatly elevated in these cells taken from subjects with type 2 DM. Patients with type 2 DM also face the effects of the hyperglycemia state, which further worsen insulin deficiency and insulin resistance. The resultant glucotoxicity can elevate the risk of developing long term complications, including microvascular disease as well as macrovascular disease. Uncontrolled hyperglyceamia is tightly linked to polyuria and glycosuria and contributes to both the pathophysiology and complications of type 2 DM. Although both unchecked hyperglycemia and the therapeutic blockade of renal glucose reabsorption share the manifestation of glycosuria, only SGLT2 inhibition involves lowering of the renal glucose excretion threshold, which functions to reduce the level of hyperglycaemia. Suppressing glucose reabsorption, through blockade of SGLT, would increase UGE, thereby reducing plasma glucose levels and potentially offering a novel therapeutic strategy, without the adverse effects that accompany currently available agents for type 2 DM.[50]

DEVELOPMENT OF SGLT2 INHIBITORS

Phlorizin

Phlorizin is comprised of a glucose moiety and two aromatic rings joined by an alkyl spacer and this agent was first isolated in 1835 by French chemists from the root bark of the apple tree and was subsequently found to be a potent but relatively non-selective inhibitor of both SGLT2 and SGLT1.[51]

Rossetti and his team compared the effects of phlorizin on blockade of renal glucose reabsorption in diabetic rats in which diabetes had been induced by partial pancreatectomy with controls. Using euglycaemic hyperinsulinaemic clamp studies, phlorizin was found to normalize insulin sensitivity in these diabetic rats but did not influence insulin action in controls.[52] Administration of phlorizin resulted in glycosuria which normalized both the fasting and fed plasma glucose levels and completely reversed insulin resistance. When phlorizin was discontinued, hyperglycaemia & insulin resistance recurred. This study was the first demonstration that hyperglycaemia alone can lead to the development of insulin resistance via glucotoxicity.

Phlorizin was used in multiple subsequent investigations that helped to establish that hyperglycaemia contributes to the insulin resistance that characterizes type 2 DM. Although studies revealed that phlorizin administered orally to mice blunted the increase in blood glucose levels after ingesting a glucose solution, it was not further developed as a possible anti-diabetes therapy due to poor

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intestinal absorption and resultant low bioavailability as well as rapid in vivo ß-glucosidase degradation. Another significant disadvantage is that phlorizin also acts on SGLT1, which is mainly expressed in the gastrointestinal tract. SGLT1 gene mutations lead to glucose and galactose malabsorption, dehydration and diarrhea. A third drawback is when phlorizin is hydrolysed in the gut, phloretin is produced which inhibits facilitative glucose trasporters such as GLUT1. Suppression of intestinal GLU1 impairs intestinal transport of glucose and results in gastrointestinal side effects such as diarrhoea.[53]

Development of Farxiga (dapagliflozin)

Despite the limitations of phlorizin, interest in SGLT inhibition was renewed in the late 1980_s when Rossetti et al. demonstrated that phlorizin-induced urinary glucose excretion reduced hyperglycemia in animals and normalized insulin sensitivity and ß-cell function as a result of reduced glucotoxicity. The first class of SGLT2 inhibitors with O-glycoside linkages modeled after phlorizin were still susceptible to degradation in vivo. However, the next generation of SGLT2 inhibitors with C-glycoside linkages, the first of which was dapagliflozin, showed metabolic stability in vivo consistent with once-daily dosing, increased oral bioavailability, potency and selectivity for SGLT2.

Dapagliflozin (developed by Bristol-Myers Squibb and AstraZeneca), which is the furthest advanced compound in development in the SGLT2 inhibitor class, once-daily, oral treatment for type 2 DM. C-aryl glucoside linkage found in dapagliflozin confers resistance to degradation in the gastrointestinal tract by ß- glucosidase enzymes. In addition, it is approximately 1,200-times more selective for SGLT2 over SGLT1. A 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.

Dapagliflozin has 84% bioavailability in rats and pharmacological half life of 4.6 h. Dapagliflozin circulates bound to albumin and at a plasma concentration of $10\mu_M$, the free fraction is 3 and 4% in rat and man, respectively.[54]

SAFETY OF SGLT2 INHIBITION

One of the major safety concerns of many diabetes agents is the potential development of hypoglycaemia. However, given that SGLT2 inhibitors act independently of glucose-dependent insulin secretion by the pancreatic ß-cells and that they incompletely inhibit glucose reabsorption, this type of adverse effect is not expected.

Although the risk of hypoglycaemia is low, it is important to investigate its potentials development if SGLT2 inhibitors are administered in combination with other anti-diabetic agents, such as metformin or the insulin secretagogues. Given mechanism of action of SGLT2 inhibitors, other safety issues include the development of urinary tract infections and fungal genitourinary infections, as well as deterioration of renal function.

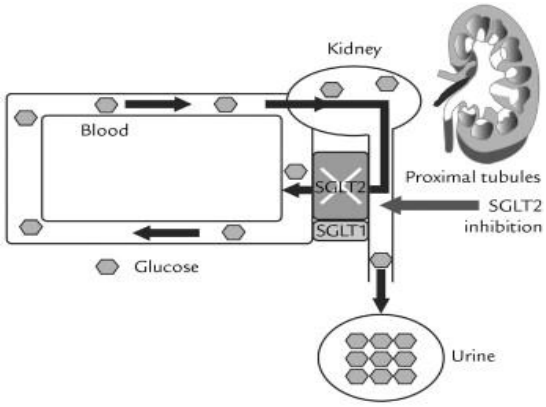

Fig: 5 mechanism of action of SGLT2 inhibition

Familial renal glycosuria is characterized by persistent isolated glycosuria of approximately 10-120 g per day, in the face of normal fasting

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serum glucose, normal glucose tolerance tests, and the absence of any signs of general renal tubular dysfunction or other pathological changes and normal life expectancies. Individuals with familial renal glycosuria usually report no complaints, and only rarely have hypoglycaemia or hypovollaemia.[55]

CONCLUSION

SGLT-2 is a molecular target to directly induce glucose excretion and to safely normalize plasma glucose in the treatment of type 2 diabetes. SGLT2 inhibitors increase the glucose excretion and control the blood sugar level without any risk of hypoglycemia and weight gain. SGLT2 inhibitors offer several advantages over other classes of hypoglycemic agents. Due to their insulin-independent mode of action, SGLT2 inhibitors provide steady glucose control without major risk for hypoglycemia and may also reverse β-cell dysfunction and insulin resistance. Other favorable effects of SGLT2 inhibitors include a reduction in both body weight and blood pressure. SGLT2 inhibitors are safe and well tolerated and can easily be combined with other classes of antidiabetic medications to achieve tighter glycemic control. The long-term safety and efficacy of these agents are under evaluation.

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