Review Article

Therapeutic Approach of Sodium Glucose Co-TransporterInhibitors to reduce Mortality and Morbidity in Type 2 DM Patients with Cardio Vascular Disorders

Abstract:

Diabetes mellitus is a metabolic syndrome, characterized by inadequate control of blood glucose levels and it is classified into Type 1, Type 2, maturity-onset diabetes of the young (MODY), gestational diabetes, neonatal diabetes, and steroid-induced diabetes. As per the epidemiological data, 537 million adults of the age between 20-79 years age-old are suffering from diabetes. Diabetic mellitus is one of the major risk factors for cardiovascular disease (CVD), people with type 2 diabetes mellitus (T2DM) have higher cardiovascular morbidity and mortality.T2DM leads to an increased risk of cardiovascular disease, with diabetes-induced micro and macrovascular complications is that major causes of morbidity and mortality in patients with T2DM. whose of 102 studies found that T2DM was associated with a 2-fold increased risk of vascular diseases such as coronary heart disease and stroke, independent of other risk factors including age, sex, smoking, body mass index, and systolic BP. The kidney's role in the reabsorption of glucose from the glucose filtrate has led to an investigation of SGLT2 as a potential therapeutic target for T2DM. SGLT2 inhibitors decrease the capacity of the proximal tubule to reabsorb glucose from the glomerular filtrate. Clinical studies have shown that SGLT2 inhibitors improve glycemic control when employed in patients with both early and late stages of T2DM.SGLT2 inhibitors have the potential to reduce CV risk in patients with T2DM not only through beneficial effects on glycemic control, but also via beneficial effects on body weight, bp, lipids, and serum uric acid.

Keywords: SGLT2 Inhibitors, Antidiabetic Therapy, Cardio Vascular Complications

Introduction:

Diabetes mellitus is one of the oldest metabolic syndromes since 1988. [1] It is a disease of inadequate control of blood glucose levels, it is classified into type 1, type 2, maturity-onset diabetes of the young (MODY), gestational diabetes, neonatal diabetes, and steroid-induced diabetes. Type 1 and 2 Diabetes mellitus are the main subtypes. Type 2 DM (formerly known as non-insulin dependent DM) is the most common form of DM characterized by hyperglycemia, insulin resistance, and relative insulin deficiency [2].

As per the epidemiological data, 537 million adults of the age between 20-79 years age-old are living with diabetes i.e., 1 in 10 persons. It is expected to have 783 million cases by the year 2045. [3]

Generally, Type 2 DM is primarily because of lifestyle factors and genetics. Lifestyle factors such as physical inactivity, sedentary lifestyle, cigarette smoking, and generous consumption of alcohol is known to be important to the development of type 2 DM. [4]

Diabetic mellitus is one of the major risk factors for cardiovascular disease (CVD), people with type 2 diabetes mellitus (T2DM) have a higher cardiovascular morbidity and mortality, and are disproportionately affected by CVD compared with non diabetic patients. [5] The patients with T2DM without any history of CAD have the similar risk of cardiac events as a subject with a prior myocardial infarction. [6]

Observational studies demonstrate that increased risk of heart failures in individuals with DM compared with those without DM. As per the Framingham Heart Study, DM was associated with a nearly 2-fold increase in the risk of incident HF in men and a 4-fold increase in women, even after adjustment for other cardiovascular risk factors. [7]

PATHOGENESIS OF T2DM AND LIMITATIONS OF CURRENT THERAPIES

T2DM results from the progressive dysfunction of β-cell due to chronic insulin resistance, which leads to a decrease in plasma glucose control. [8] During the pathogenesis of T2DM the signalling pathways are disrupted which generally involves glucose homeostasis, which results in increased glucagon secretion, reduced incretin response, increased endogenous glucose production, increased renal glucose reabsorption, impaired expansion of subcutaneous adipose tissue, and hypoadiponectinemia. [9] There are many therapies available for the treatment of patients with T2DM which involves increasing insulin sensitivity or by stimulating insulin secretion. [10]

Achieving target levels of glycated haemoglobin (HbA1c) with low rates of hypoglycemic events is considered to be the success of treatment [10]. Initially, the management consists of lifestyle modifications which include diet and exercises often with metformin monotherapy at the time of diagnosis. More complex treatment regimens are prescribed once the disease progresses further in which it involves more than one antidiabetic agent and ultimately insulin, which are required to keep plasma glucose levels at target [11]. This can be observed as a "treat-to-failure" approach, and results in patients having abnormal glycemic control for much of their time on treatment [12].

Recent developments and strategies have focused on "individualizing" treatment for patients in the context of wider disease management [13].

This patient centred approach to care goes beyond algorithms to incorporate patient attituded and preferences, gender, race, ethnicity, risks of therapy, comorbidities, the presence of complications, and the resources and support systems available to the individual [14].

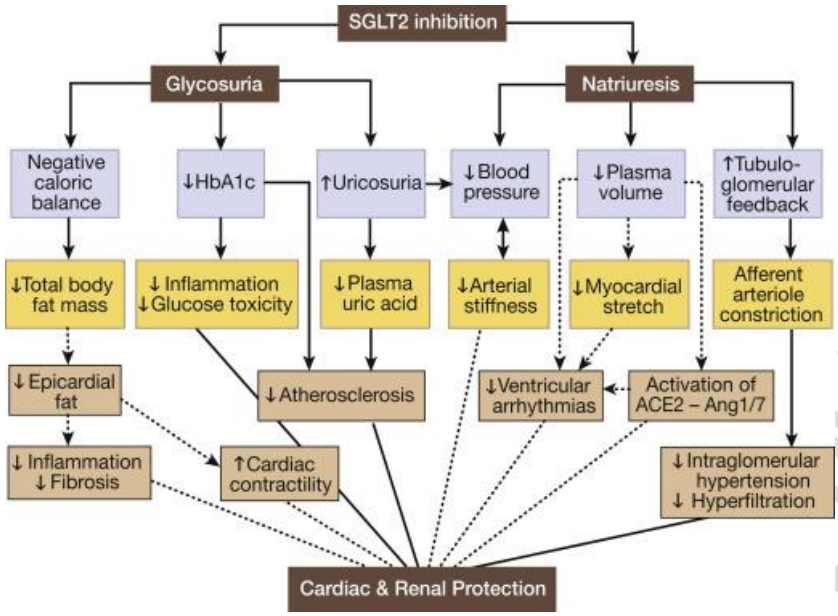

Figure 1. **Possible mechanisms responsible for cardiovascular and renal protection with sodium–glucose cotransporter 2 (SGLT2) inhibition.** Solid lines represent pathways supported by existing data; dashed lines represent possible areas for future research. ACE2, angiotensin-converting enzyme-2; Ang1/7, angiotensin 1/7; HbA1c, haemoglobin A1c.

T2DM AND CVS RISK:

T2DM leads can increased risk of vascular disease, with diabetes induced micro and macro vascular complications is the major causes of morbidity and mortality in patients with T2DM [(15)]. A meta -analysis of 102 studies found that T2DM was associated with a 2-fold increased risk of vascular diseases such as coronary heart disease and stroke, independent of other risk factors including age, sex, smoking, body mass index, and systolic BP [(16)]. Large clinical studies of the effects of intensive glucose decreasing the mortality and CV outcomes in patients with T2DM have not proved to be straight forward, suggesting that the relationship between the two is complex and not only related to control of hyperglycaemia. Recent data (e.g., from the ACCORD, VADT and ADVANCED trials) have demonstrated modern but significant microvascular benefits with aggressive glucose control. However, in these same studies, aggressive glucose control did not decrease macrovascular outcomes in patients with

characteristics such as long-standing disease, advanced age and frailty, low awareness of hypoglycemia, significant comorbidities, and /or pre-existing macrovascular disease [17,18,19,20,21]. In addition to hyperglycemia many patients with T2DM have comorbid conditions that elevates the risk of CVD. The comorbidities include obesity, hypertension and dyslipidemia and other inter related epidemiologically, clinically and metabolically [21].

It is estimated that approximately 90% of T2DM cases are attributable, at least in part, to excess body weight [22] and obesity. Hypertension is also common in patients with T2DM and is a significant risk factor for CVD in this patient group [23]. Atherosclerosis and T2DM leads to vascular damage and share common causative mechanisms (including inflammation) and risk factors, including hypertension and dyslipidemia [24].

T2DM is a multifractional disease, the effects of antidiabetic agents' pathophysiological abnormalities other than hyperglycemia may not show greater consideration than they have received to the date [25]. Some CV risk factors example hypertension are modifiable with intervention and represent a legitimate strategy for addressing the high CV mortality in patients with T2DM [26]. It is important to note that effects of antidiabetic therapies on CV risk factors may have either a positive (e.g., reduction in BP, weight loss) or negative (e.g., weight gain, increased hypoglycemia) effect (Table 1).

Table 1 Effect of antidiabetic drugs on CV risk factors [27]

Intervention	CV Risk Factor					
	HbA1c	Body Weight	Hypertension	Edema	Dyslipidemia	Hypoglycemia
Metformin	Improvement	Loss/neutral	Neutral	Neutral	Improvement	Low risk
Sulfonylureas	Improvement	Gain	Neutral	Neutral	Variable	Moderate risk

Thiazolidinediones (Glitazones)	Improvement	Gain	Improvement	Moderate risk of peripheral Edema	Improvement	Low risk
Meglitinides (Glinides)	Improvement	Gain	Neutral	Neutral	Neutral	Moderate risk
α-glucosidase inhibitors	Improvement	Neutral	Improvement	Neutral	Neutral/ Improvement	Low risk
DPP-IV inhibitors (gliptins)	Improvement	Loss/ neutral	Neutral	Neutral	Improvement	Low risk
GLP-1 receptor agonists	Improvement	Loss	Improvement	Neutral	Improvement	Low risk
Insulin	Improvement	Gain	Hyperinsulinemia is associated with	Acute insulin Edema (rare)	Improvement	High risk
SGLT2 inhibitors [(a)]	Improvement	Loss	Improvement	Neutral	Limited Data	Low risk

PHYSIOLOGY OF SODIUM GLUCOSE COTRANSPOTERS:

In glucose homeostasis, kidneys play an important role, normally accounting for more than 10% of total glucose utilization in the body, up to 20% of all glucose production via gluconeogenesis, and, most importantly mediating the reabsorption of glucose from the glomerular filtrate [27 ,28]. T2DM augments all of these functions of the kidney. A three-fold increases in overall glucose production has been observed in patients with T2DM, with both the liver and the kidneys contributing to these increases via gluconeogenesis [28]. Renal glucose reabsorption is increased [27]. In healthy adults with a glomerular filtration rate of -125 Ml /min, approximately180L of plasma is filtered through the kidneys every day [27]. A healthy adult with an average plasma glucose concentration of 5 mmol/L filters approximately 180g of glucose per day into the glomerular filtrate [27]. Sodium glucose cotransporters (SGLTs) will filtrate all the glucose in the kidney [29]. SGLT2 is located in the proximal tubule of the nephron and accounts for approximately 90% of renal glucose reabsorption [28]. This operates by coupling glucose transport to an electrochemical sodium gradient to move glucose and sodium ions across the luminal surface3 of the epithelial cells lining the S1 and S2 segments of the proximal tubule [29]. When the glucose is concentrated in the epithelial cells it is transported into blood, facilitated by the glucose transporter GLUT2 [29,30]. Reabsorption of glucose from the glomerular filtrate increases in proportion to the plasma glucose concentration until the maximum transport capacity of the tubules is reached, above which excess glucose is lost in the urine [28]. In people with T2DM, the transport maximum for glucose (TmG) is increased up to 20%, and urinary glucose excretion begins to occur at higher-than-normal plasma glucose

levels [27]. Studies of renal cells isolated from urine have shown that SGLT2 and GLUT2 expression is increased in patients with T2DM [31].

SODIUM-GLUCOSE COTRANSPOTER INHIBITORS USED IN T2DM:

Kidney's role in the reabsorption of glucose from the glucose filtrate as led to the investigation of SGLT2 as a potential therapeutic target for T2DM. SGLT2 inhibitors decrease the capacity of the proximal tubule to reabsorb glucose from the glomerular filtrate, leading to increased urinary glucose excretion, which reduces hyperglycemia [30]. Many

SGLT2 inhibitors are now in phase III clinical development (table 2). Dapagliflozin, the first agent submitted for approval, was rejected by the FDA in January 2012.

EFFICACY AND SAFETY OF SGLT2 INHIBITORS IN PATIENTS WITH T2DM:

Clinical studies of monotherapy with SGLT2 inhibitors in patients with T2DM have shown reductions from baseline in HPA1c starting from 0.63% -1.45% [32,33,34]. SGLT2 inhibitors are oral therapies with a mode of action that does not interact with glucose metabolism. Therefore, they might be expected to enrich insulin-dependent therapies in T2DM, which has been borne in clinical studies demonstrating the efficacy of SGLT2 inhibitors when utilized in combination with antidiabetic agents. Additional reductions in HBA1c of up to 0.73% are observed when an SGLT2 inhibitor has been added to metformin [27,35,36,37,38]. When utilized in combination with glimepiride, dapagliflozin reduced HBA1c by up to 0.82%, compared with a discount of 0.13%with glimepiride alone [39], while with pioglitazone, dapagliflozin reduced HBA1c by up to 0.97%, compared to a discount of 0.42% with pioglitazone alone [42]. Dapagliflozin + insulin reduced HBA1c by up to 0.96%, versus a discount of up to 0.13% achieved with insulin alone [41,42], and similar results are observed with canagliflozin [43]. SGLT2 inhibitors are shown to cut back fasting plasma glucose (FPG). Used as monotherapy, reductions in FPG within the order of 15-65mg/dl are observed in clinical trials [32,33,34,44,45,46,47]. When utilized in combination with metformin, additional reductions of up to 32.7md/dl are seen [27,36,37,44,38], together with glimepiride alone [39]. With pioglitazone, dapagliflozin reduced FPG by 24.9-29.6mg/dl compared with a discount of 5.5mg/dl with pioglitazone monotherapy [40]. A mixture of dapagliflozin + insulin reduced FPG by 15.4-27.4mg/dl over insulin alone [41], While canagliflozin plus insulin reduced FPG by a further 42.7-44.7 mg/dl over insulin alone [43]. In addition to decreasing FPG, SGLT2 inhibitors reduce the postprandial spike in plasma glucose concentrations. Reductions in postprandial glucose (PPG) are observed with SGLT2 inhibitors used as monotherapy or together with sulfonylurea (SU), pioglitazone or insulin therapy [39,40,41,46]. As SGLT2 inhibitors work independently of insulin, the efficacy of those drugs is independent of ß cell function or insulin resistance [48]. Clinical studies have shown that SGLT2 inhibitors improve glycemic control when employed in patients with both early and late stages of T2DM. The number of

cases of breast and bladder cancer was too small as certain causality. There is no known connection between SGLT2 inhibition and tumor risk in life time exposure studies in animals, dapagliflozin failed to increase the incidence of any tumor [49].

The potential of SGLT2 inhibitors to reduce CV risk in patients with T2DM:

SGLT2 inhibitors have the potential to reduce CV risk in patients with T2DM not only through beneficial effects on glycemic control, but also via beneficial effects on body weight, bp, lipids, and serum uric acid.

- **Body Weight**

Weight loss in patients with T2DM has been shown to be associated with improvements in CV risk factors, including hyperglycemia, hypertension, and markers of inflammation. [50]

In patients treated with SGLT2 inhibitors, loss of glucose in the urine results in loss of calories and a reduction in body weight, initial weight loss may also reflect some fluid loss as UGE results in mild osmotic diuresis. [30]

Weight reductions of ~1-3.8kg have been observed with SGLT2 inhibitor monotherapy in clinical trials in patients with T2DM. [51]

Reductions have also been observed when SGLT2 inhibitors are used in combination with metformin, SU, pioglitazone or insulin. [52]

- **Blood pressure**

Reductions of BP in patients who take SGLT2 inhibitors are believed to be due, at least in part, to mild osmotic diuresis, as urine output increases due to lower reabsorption of water in kidneys. Initial increases in urinary volume up to 450ml/day have been reported after dapagliflozin treatment. [53]

This represents one extra void per day, but these levels are off, and signs of volume depletion such as orthostatic hypotension and tachycardia have been reported very rarely. [27]

Reductions in weight and sodium ion excretion may also contribute to BP reductions. [54]

Maximum mean reductions in systolic BP of 3-9mmHg have been observed in studies of SGLT2 inhibitors used as monotherapy [56] and in combination with metformin, SU or pioglitazone [27].

❖ **Lipids**

Small volume changes are reported in some trials of SGLT2 inhibitors. Increases in total cholesterol and HDL cholesterol [35]. With canagliflozin, increases in HDL cholesterol and LDL cholesterol are observed, with a minimal effect on the entire cholesterol: HDL cholesterol ratio, and little and inconsistent changes in triglycerides. [55]

❖ **Uric Acid**

Small reductions (approximately 1mg/dl) in serum acid are reported in trials of SGLT2 inhibitors used as monotherapy [44]

Reductions in serum acid levels could also be mediated by GLUT9 (SLC2A9), a facilitative glucose transporter within the proximal tubule. GLUT9 functions as a high-capacity urate transporter and is believed to secrete acid into the tubule in exchange for luminal glucose. [56]

Thus, an increased glucose concentration within the proximal tubule would be expected to extend the secretion of uric acid into the urine and reduce serum acid. Reduction in serum acid could have beneficial effects on CV risk, given the increasing evidence that elevated serum acid levels are an independent risk factor for CV disease [57].

Overall Remarks:

Hazard of serious unfriendly occasions related with the utilization of SGLT2 inhibitors. SGLT2 inhibitor use was related with two-fold expansions in the gamble of both lower appendage removal and diabetic ketoacidosis, however no recognizable expansion in risk was noticed for the other examined antagonistic occasions. The discoveries are conflicting with an overall gamble increment of over 33% for bone break, 5% for intense kidney injury, 19% for

serious urinary lot contamination, 38% for venous thromboembolism, and 112% for intense pancreatitis.

Discussion:

SGL2 Inhibitors are one of the best choices of drugs in treating patients with Type 2 DM who are underlying cardiovascular diseases. These inhibitors generally involve exerting favorable effects beyond glucose control such as consistent body weight, blood pressure, and serum uric acid reductions. Canagliflozin, Dapagliflozin, and empagliflozin belong to the class of SGL2 Inhibitors. But however, it also has unwanted adverse effects. The incidence of adverse events in clinical trials of SGLT2 is the same as observed with other anti-diabetic drugs. The overall incidence of adverse events has ranged from 57.3 to 83.0%, while that of serious adverse events has varied between 1.0% and 12.6%, which can be minimized with the rationale approach of the therapy.

Conclusion:

By analysing various research articles, it was found to be Sodium Glucose Co-transporter (SGLT2) Inhibitors are the rational approach to treat Type 2 DM patients with Cardio Vascular complications, because the evidences proved SGLT2 inhibitors are directly acting on various parameters to reduce the cardio vascular risks and decrease the mortality and morbidity of the Type 2 DM patients with CV disease.

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