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Research Article

Paradoxical Additional Role of SGLT2 Inhibitors Beyond Glycosuria in Controlling Obesity, NAFLD Treatment, Pancreatic β Cell Protection Besides Therapy for Diabetes Mellitus, CVOT and Renoprotection-A Minireview

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Abstract

Earlier we had reviewed how obesity is assuming an endemic/pandemic proportions resulting in escalating incidence as well as prevalence associated with escalating worldwide incidence of metabolic syndrome (MetS) with non-alcoholic fatty liver disease (NAFLD), that is correlated with enhanced morbidity. We tried to detail how probiotics, L-carnitine (LC), nicotinamide ribose (NR) combination, along with apical sodium dependent bile acids transporter (ASBT) or volixibat and silybin, vitamin D, allyl isothiocyanate (AITC), might aid in treating and understand the etiopathogenesis of NAFLD, besides role of Astragaloside IV. Having reviewed sodium-glucose cotransporter 2 (SGLT2) inhibitors earlier for better glycaemic control and cardiovascular outcome (CVOT) and renoprotective actions here we conducted a minireview on how SGLT2 inhibitors have demonstrated certain magical actions beyond glycosuria for Diabetes mellitus (DM) control, in treating obesity, protective action on pancreatic β cells and how they are another efficacious therapy for NAFLD specifically in the ones who have developed diabetes mellitus (both type 1 and 2).

Keywords: T2DM; T1DM; Empagliflozin; Canagliflozin; NAFLD; Obesity

Introduction

Globally the escalation of obesity with associated enhancement of type 2 diabetes mellitus (T2DM) incidence has become a concerning problem secondary to lifestyle alteration, so much so that it has been decided to treat the two together as diabesity [1]. As sodium-glucose cotransporter 2 (SGLT2) aids in maximum of renal glucose reabsorption, inhibition of SGLT2 is attractive for T2DM treatment [2-5]. Earlier we had reviewed how obesity is assuming endemic/pandemic proportions resulting in escalating incidence as well as prevalence associated with escalating worldwide incidence of metabolic syndrome (MetS) with non-alcoholic fatty liver disease (NAFLD), that is correlated with enhanced morbidity. We tried to detail how probiotics, L-Carnitine (LC), nicotinamide ribose (NR) combination, along with apical sodium dependent bile acids transporter (ASBT) or volixibat and silybin, vitamin D, allyl isothiocyanate (AITC), might aid in treating and understand the etiopathogenesis of NAFLD [6-12]. Here we further updated how astonishingly SGLT2 inhibitors have exhibited multiple roles beyond anticipation as a magical therapy, in a way that it possesses action that is much greater than its intended uses as an anti-diabetic agent in view of its action of enhancement of glycosuria. SGLT2 inhibitors confer protection to the pancreatic β cells from glucose toxicity along with amelioration of insulin resistance (IR), that ultimately abrogates glycaemic regulation. Furthermore, whereas non-alcoholic fatty liver disease (NAFLD), it has got demonstrated that SGLT2 inhibitors mitigate NAFLD. Having reviewed earlier with regard to therapy of NAFLD in addition to SGLT2 inhibitors [13-16], we aimed to conduct this minireview with the idea of demonstrat-

ing how SGLT2 inhibitors aid further in protection of pancreatic β cells, besides controlling the blood sugars in diabetes mellitus for which initially they were discovered with their actions of promoting glycosuria from kidney, along with emphasizing further in treatment of NAFLD, besides other additive actions in obesity with regards to escalation of weight reduction, along with them being cardio along with renoprotective in addition to being useful for T1DM as an adjuvant.

Methods

Thus a review was carried out using the pubmed, Web of Science, Medline, Embase, Cochrane reviews and Google Scholar, Search engine with the MeSH Terms; impaired lipid metabolism; oxidative stress; inflammation; T2DM); Type 1 diabetes (T1D); SGLT2 inhibitors; empagliflozin; canagliflozin; NAFLD; obesity; pancreatic β cells; glucose toxicity; CVS protection; renoprotection in T2D and of T1D from last 10 yrs from 2010 till date upto 2021 to update on treatment of NAFLD, besides other multiple roles of SGLT2 inhibitors besides glycosuria like pancreatic β cells protection and its role in obesity therapy. Both animal and human studies were included for this update.

Results

We found a total of 750 articles, out of which we selected 66 articles for this review. No meta-analysis was done. Basically, the results are based on human studies only following corroboration by animal studies as well (Figure 1 on selection criteria). The reason why only limited articles were selected here was that idea was just to update what we had not included in our earlier reviews with regards to actions of SGLT2 inhibitors in CVOT5Trials like combination with metformin, use in T1D as well as in the epigenetic article-see figure 1.

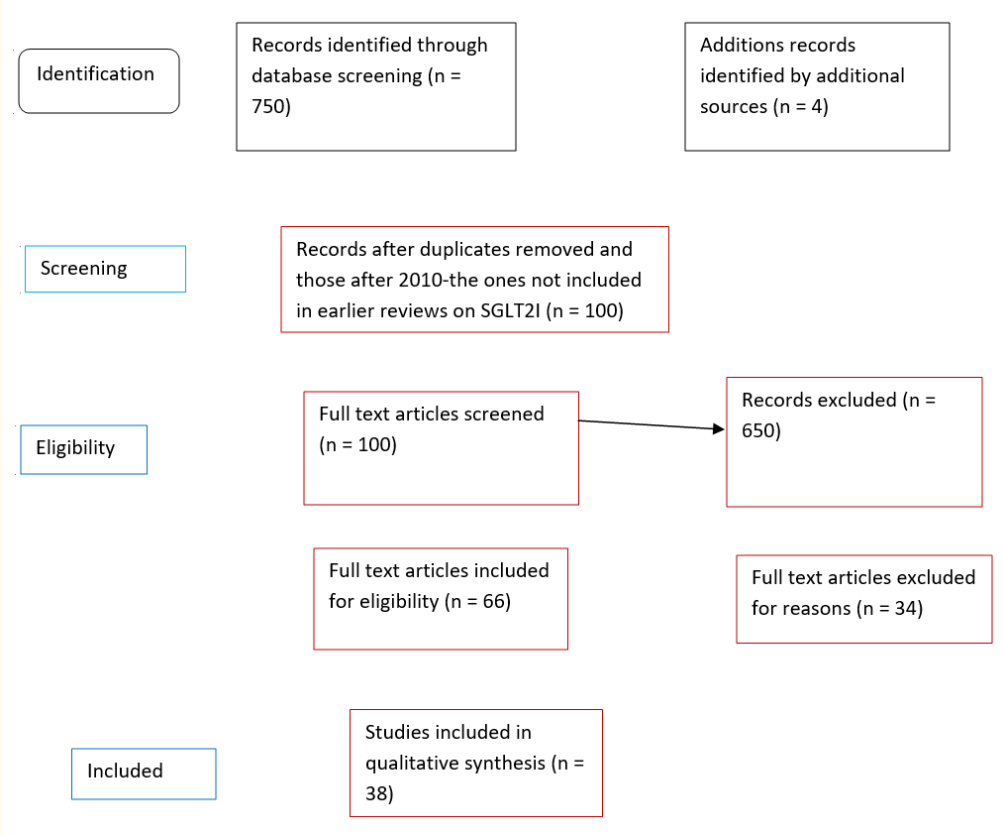

Figure 1: Screening criteria.

Posit of pancreatic β cells glucose toxicity observed in type 2 diabetes mellitus

The basic properties of T2DM are inadequate insulin liberation along with insulin resistance (IR). In healthy situations, blood glucose amounts are well regulated by insulin, whereas in diabetic situations, escalated IR results in dysfunctional insulin generation as well as liberation. i) IR gets initiated either by excessive food consumption, as well as/or no exercise, although adequate insulin gets liberated that compensates for the IR. Nevertheless, on exposure of βcells to raised glucose amounts for a long duration, β cells function gets depleted gradually in view of extra load. Insulin generation as well as liberation reduce in addition to Insulin genes transcription factor MafA along with PDX1 [17-21] (Figure 1). Ultimately β cell amounts get reduced by apoptosis as well as/or, de-differentiation. These events are labeled as glucose toxicity. Nevertheless, it has been illustrated, that β cells function gets resurrected by a proper therapy with different anti diabetic drugs [22-24]. Chronic hyperglycemia further interferes with insulin signaling in insulin target tissues, that result in the propagation of insulin resistance. Hence glucose toxicity is implicated in IR, besides β cells impairment.

MafA is a strong insulin gene transcription factor [17-19]. Expression of MafA amounts is significantly reduced under diabetic situations, but it gets conserved following diminishing of glucose toxicity with anti-diabetic drugs. Moreover Kaneto D., *et al*. [21], documented that serum insulin amounts were escalated besides blood glucose getting reduced via conservation of expression of MafA in βcells in obese type 2 diabetic db/db mice with the utilization of Cre-lox P System. Additionally, β cells mass got conserved via overexpression of MafA [19]. They thought that these observations illustrated that decrease in MafA expression results in β cells impairment observations seen in T2DM. PDX1 further represents insulin genes transcription factor, along with, possessing significant part in the β cells. Nevertheless, its expression amounts fall following exposure to chronic hyperglycemia [17,18]. Kaneto., *et al*. [21], believed that decrease of PDX1 further results in β cells impairment observed in T2DM. Actually glucose-induced insulin liberation was escalated, besides glycaemic regulations got abrogated by conservation of PDX1 expression in β cells with the utilization of Cre-lox P system [20]. In toto, they thought that decrease in MafA along with PDX1 expression results in β cells impairment observed in T2DM.

Moreover, whereas various documents pointed to the part of insulin signaling in endothelial cells [25,26], it is further presumed that endothelial impairment is further correlated with β cells impairment. It had been presumed that as pancreatic islets get destroyed with ease by ischaemia, or different stresses, β cells impairment results secondary to endothelial impairment. Indeed recently it was revealed that vascular endothelial cells-particular knock out of PDK1, that is one of the most significant molecules in insulin signaling, β cells impairment, got combined together with impairment of vascularity in islets, which get into ischaemic state, in addition to inflammation as well as endoplasmic reticulum (ER) stress in β cells [26]. As this type of phenotypes are akin to this event under diabetic situations, it is assumed that endothelial impairment is further correlated with β cells impairment observed in T2DM.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors mitigate hyperglycemia via escalation of urinary glucose excretion

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are usually utilized for T2DM patients all over the world [2-4,13]. SGLT2 inhibitors result in abrogation of glycemic regulation by escalation of urinary glucose excretion. Additionally, it is accepted that under diabetic situations expression of SGLT2 in the kidney gets escalated, resulting in glucose reabsorption, escalating worldwide proof exists as per the safety in addition to effectiveness of SGLT2 inhibitors in T2DM patients. Tofogliflozin possesses a great specificity for SGLT2 while canagliflozin possesses least specificity [27], despite a controversy persisting its significance in our human bodies. Additionally, dual SGLT2 inhibitors got generated with advantageous actions. It got documented that dual SGLT2 inhibitors escalated glucagon like peptide 1 (GLP-1) amounts, besides decreasing post prandial glucose amounts [28].

SGLT2 inhibitors possess advantageous actions on pancreatic β cells

That SGLT2 inhibitors confer protection on pancreatic βcells from glucose toxicity has been demonstrated [29-34]. Actually, it got documented that a SGLT2 inhibitor luseogliflozin did conserve pancreatic function in case of obese type 2 Diabetic db/db mice [33]. Significant enhancement of pancreatic β cell mass was observed on utilization of luseogliflozin therapy. Additionally, escalation of β cells proliferation, in addition to reduction of βcells apop-

tosis was further observed with this therapy. Insulin generation, in addition to escalation of expression amounts of MafA along with PDX1 [35]. Overall SGLT2 inhibitors possess a promising action on preservation of βcells action (Figure 2).

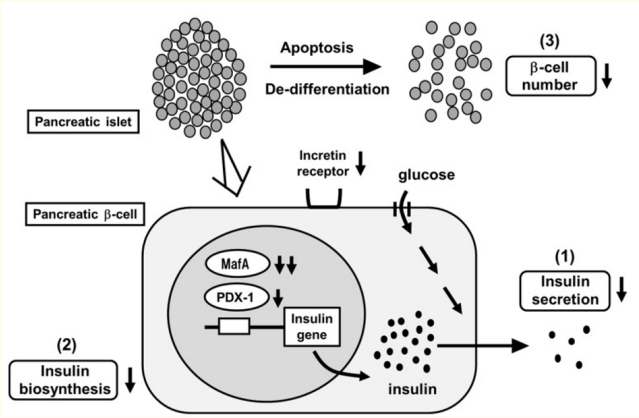

Figure 2: Courtesy ref no-21-Pancreatic β-cell glucose toxicity found in type 2 diabetes mellitus (T2DM). When pancreatic β-cells are exposed to chronic hyperglycemia, β-cell function gradually declines. First, insulin secretion is reduced. Second, insulin biosynthesis is reduced together with reduction of MafA and PDX-1 expression. Third, β-cell number is decreased through the process of apoptosis and/or de-differentiation.

Besides that, for getting insight on direct actions of SGLT2 inhibitors on β cells, researchers conducted certain experiments for just 1 week with empagliflozin [32]. No implications on lipid metabolism took place, although empagliflozin protected βcells. Escalation of insulin, MafA along with PDX1 expression was observed further with empagliflozin therapy. From these results it is obvious that SGLT2 inhibitors directly confers protection on βcells from glucose toxicity [32] (Figure 2).

Moreover, recently Kimura., *et al*. tried to contrast the action of luseogliflozin in conferring protection on β cells mass in addition to function among early as well as at late stage of diabetes, besides among short term utilization along with, long term utilization of this agent with the utilization of Diabetic db/db mice [34]. As far as the results were concerned, pancreatic β cell mass was preserved with luseogliflozin therapy at an early stage of the DM by luseogliflozin but not enhanced during late stage of diabetes. Furthermore, β cell mass was escalated by this type of treatment only during early stage. Moreover, on treatment of Diabetic db/db mice with luseogliflozin for a long time period from an early stage of the disease, the long utilization of SGLT2 inhibitors possessed a greater advantageous actions with insulin generation in addition to liberation was conserve, even during the enhanced or late stage [34]. In toto, SGLT2 inhibitors possess greater advantageous actions on β cells in contrast to short term utilization (Figure 2).

Whereas different studies got conducted actively with regard to the part of α cells [35], it got demonstrated that SGLT2 existed in α cells in addition to dapagliflozin escalated glucagon liberation, resulting in escalated hepatic gluconeogenesis [36]. Despite this escalation, blood glucose amounts got reduced by dapagliflozin, possibly secondary the escalation of glycosuria. In healthy mice further, it was demonstrated that dapagliflozin escalated glucagon liberation in addition to hepatic gluconeogenesis, that restricted the blood glucose amounts stimulated by fasting [36]. Noticeably, nevertheless, the issue of direct actions of SGLT2 hampering on glucagon liberation continues to be a controversial topic. Like a group illustrated that SGLT2 expression in human islets believed that dapagliflozin directly induced glucagon liberation via SGLT2 hampering on α cells [36], while another group demonstrated that SGLT2 expression was not seen in human or mouse islets [37]. Very recently, the significance of SGLT2 actions on glucagon liberation got analysed by utilization of perfused rat pancreas. The outcomes illustrated that glucagon liberation got reduced by escalated glucose, but that was not influenced by SGLT2 inhibitors, that explains glucose effect was not secondary to a direct action of SGLT2 on α cells [38].

SGLT2 inhibitors possess advantageous actions on insulin resistance

That SGLT2 inhibitors possess advantageous actions on insulin target tissues has been the knowledge we gained. Utilization of SGLT2 inhibitors result in mitigation of fatty liver, decrease in visceral fat mass, besides amelioration of IR [39-41] (Figure 2). Actually, tofogliflozin resulted in reduction of insulin resistance, besides abrogating glycaemic control in Diabetic mice [46]. Here C57BL/6 mice received normal chow or high fat chow possessing tofogliflozin. Secondary to this tofogliflozin resulted in reduction of body weight in addition to blood glucose amounts in Diabetic mice. Additionally, adipocyte size along with fat mass decreased by

tofogliflozin, that ultimately escalated insulin sensitivity [41]. Escalated insulin liberation further got decreased in tofogliflozin recipients, that resulted in escalation of lipolysis, ultimately escalated insulin sensitivity β oxidation, as well as ketone bodies. This decrease in insulin liberation, escalated gluconeogenesis in addition to reduction of lipogenesis. This lipogenesis reduction resulted in triglycerides (TG) amounts in the liver. Moreover, hyper insulinemic euglycaemic clamp study demonstrated that IR got decreased by tofogliflozin secondary to escalated glucose uptake into the skeletal muscle [41]. Overall tofogliflozin ameliorates IR via escalated lipolysis in adipose tissue (AT), in addition to glucose uptake into skeletal muscle (Figure 2). Additionally, it got illustrated that ipragliflozin decreased fat mass basically through fatty acids (FA) β Oxidation in high fat diet (HFD) stimulated obese rats in addition to tofogliflozin led to reduction of fat collection in diet induced obesity (DIO) rats as well as KKay mice [39].

SGLT2 inhibitors have been demonstrated to possess advantageous actions on patients with T2DM also [40]. Dapagliflozin was illustrated to decrease blood glucose amounts in addition to fat mass for a long duration in patients with T2DM. Additionally, it got illustrated that dapagliflozin escalated insulin sensitivity in skeletal muscle, nevertheless it caused enhancement of hepatic glucose production (HGP) in patients with T2DM. Patients with T2DM got randomized in this study to receive dapagliflozin or placebo, as well as HGP got analysed with the aid of clamp method. Secondary to this HGP in addition to plasma glucagon got escalated by Dapagliflozin. They demonstrated that the enhancement of insulin sensitivity in skeletal muscle, but escalated HGP. It was further documented that HGP as well as glucagon amounts escalated by empagliflozin in patients with T2DM. It had been assumed by Kaneto., *et al*. [21], the escalated HGP does not essentially point to exaggeration of IR in the liver. There is feasibility that this elevation of HGP with SGLT2 therapy, is at minimum correlated with reduction of ratio of serum insulin/glucagon.

SGLT2 inhibitors possess advantageous actions on nonalcoholic fatty liver disease (NAFLD), via escalation of hyperinsulinemia

NAFLD patient amounts has escalated world over. It includes simple fatty liver to non alcoholic steatohepatitis (NASH), along with fibrosis as well as inflammation [42]. T2DM patients possess a greater chance of generation of NAFLD, with the existence of T2DM, a greater tendency towards acceleration or generation of NAFLD [43]. Further it got documented that patients with T2DM had a greater risk of progressing to liver cirrhosis as well as hepatocellular carcinoma (HCC) [44]. Earlier hepatitis C virus in addition to escalating alcohol consumption were the 2 chief aetiological factors of liver cirrhosis as well as HCC. Nevertheless, recently hepatitis C virus has acquired cure, besides it being noted that different liver ailments are attributable to subject without escalating alcohol consumption. Diabetes mellitus has assumed the status of a risk factors of generation of liver disorders, rather than hepatitis C virus in addition to escalating alcohol consumption, with malignancies currently including HCC are believed to be a complication of Diabetes mellitus, besides the classical micro as well as macro diabetic complications. Thiazolidinediones also possess advantageous actions in NAFLD [45]. Nevertheless, thiazolidinediones, despite being efficacious in NAFLD usually result in escalating body weight, thus treatment involving thiazolidinediones is not proper in patients with T2DM along with NAFLD.

Noticeably SGLT2 inhibitors possess certain advantageous actions in liver [46,47]. It got demonstrated that ipragliflozin along with pioglitazone were efficacious in patients with T2DM as well as NAFLD [46]. Patients got randomized to receive ipragliflozin or pioglitazone. Due to this the liver:spleen ratio on CT was escalated in either ipragliflozin or pioglitazone group. Diabetes markers like HbA1c as well as plasma glucose amounts were reduced akin to this in the 2 groups. Nevertheless, body weight, in addition to visceral fat area had a significant reduction in the ipragliflozin group. Furthermore, they illustrated that both drugs had promising actions on NAFLD in addition to glycaemic regulation to an akin degree in patients with T2DM as well as NAFLD [47]. Further Ito., *et al*. documented that the action of 3 oral anti Diabetic agents (Dapagliflozin, pioglitazone in addition to glimepiride) on NAFLD in a prospective clinical trial in patients with T2DM as well as NAFLD [47]. The examination of liver:spleen ratio was conducted by Kinoshita., *et al*. on computed tomography (CT). In the Dapagliflozin group significant body weight reduction in addition to visceral fat area decrease was observed along with significant escalation of adiponectin was seen in the pioglitazone group. The liver:spleen ratio was significantly escalated by dapagliflozin or pioglitazone but not with glimepiride. Nevertheless, these 2 drugs appear to possess a separate mode of action. Dapagliflozin demonstrated advantageous actions on NAFLD by amelioration of hyperinsulinemia, whereas pioglitazone implicated its actions by escalation of adiponectin amounts [47]. In toto SGLT2 inhibitors have the probability of possessing an advantageous actions on NAFLD by abrogating hyperinsulinemia.

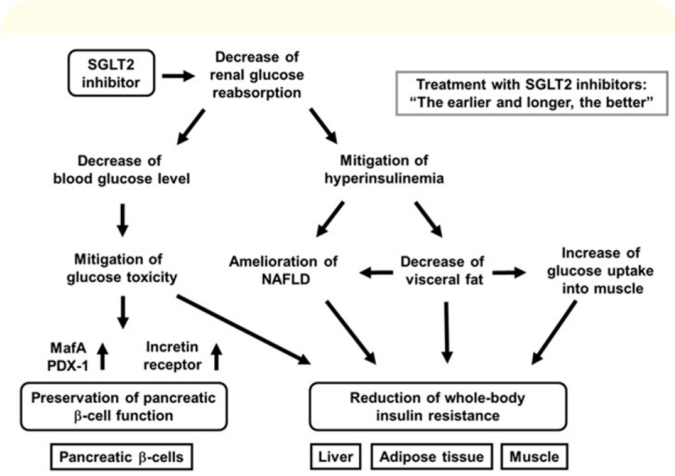

Figure 3: Courtesy ref no-21 Favorable effects of sodium-glucose cotransporter 2 (SGLT2) inhibitors on pancreatic β-cells and various insulin target tissues. SGLT2 inhibitors ameliorates glycemic control and alleviates hyperinsulinemia by reducing renal glucose reabsorption. Amelioration of glycemic control reduces glucose toxicity, which finally preserves β-cell function and mitigation of insulin resistance in insulin target tissues. Alleviation of hyperinsulinemia ameliorates fatty liver or nonalcoholic fatty liver disease (NAFLD), reduces visceral fat, and increases glucose uptake into skeletal muscle, all of which finally lead to mitigation of whole-body insulin resistance.

SGLT2 inhibitors possess beneficial cardiovascular protective actions

Utilization of different types of SGLT2 inhibitors have been done globally. Variety of clinical trials with regards to the cardiovascular protective actions of SGLT2 inhibitors have been conducted [13,14,48-52]. Like the actions of empagliflozin on cardiovascular morbidity and mortality were demonstrated in patients with type2 Diabetes mellitus in addition to great cardiovascular risk. A randomization of patients with T2DM was conducted for receipt of empagliflozin or placebo. The primary collective CVS events were documented in 10.5% patients receiving empagliflozin as well as in 12.5% patients receiving placebo. Hazard ratio (HR) in empagliflozin group was 0.86. Moreover, significant variations in rate of demise from CVS events among empagliflozin as well as placebo group (3.7% vs 5.9%), hospitalization for heart failure (2.7% vs 4.1%), in addition to mortality from any etiology (5.7% vs 8.3%). Overall, patients with T2DM receiving empagliflozin demonstrated a lesser rate of all cause mortality in contrast to the ones receiving placebo. Conversely myocardial infarction (MI) along with stroke did not get reduced much.

The CANVAS program represents another clinical trial that was conducted at a large scale, that evaluated the actions of SGLT2 inhibitors on CVS events. This program accumulated data from two trials implicating patients with T2DM with great CVS risk. In both the trials randomization of patients with T2DM was done for receipt of canagliflozin or placebo. The degree of primary collective CVS events was lesser in canagliflozin in contrast to the ones receiving placebo with regards to causing mortality. In toto canagliflozin decreases the chances of CVS events in patients with T2DM possessing an escalated risk of cardiovascular disease (CVD).

Whereas SGLT2 inhibitors reduced the overall risk of CV mortality in addition to hospitalization for heart failure in patients with or without T2DMin dapagliflozin, besides the avoidance of side effects in heart failure in DAPA-HF in addition to trials, meta-analysis of the two trials got conducted recently, where primary endpoints was time to all cause. The calculated treatment actions was a 13% decrease of all cause mortality (HR, 0.87) as well as 14% decrease in cardiovascular (CVS) death (HR, 0.86). The utilization of SGLT2 inhibitors decreased the combination risk of CVS mortality by 26% (HR, 0.74).

It is well acknowledged that heart failure (HF) predominantly affects the prognosis of patients with T2DM. HF with low ejection fraction (EF) can get treated with the utilization of diuretics in addition to/or anti-hypertensives, but no definite beneficial agent for HF with preserved EF, that has the properties of left ventricular diastolic impairment. Recently it was illustrated that SGLT2 inhibitors possess certain beneficial actions on heart failure (HF) with preserved EF, that is the property of left ventricular diastolic impairment. The diminution of proinflammatory cytokine signaling via SGLT2 inhibitors might reveal certain molecular modes. It has been realized that SGLT2 inhibitors diminish certain CVS risks by enhancing glucose in addition to lipid metabolism. Furthermore, it is well understood that hypoglycemia escalated certain CVS events, along with need of the hour is prevention of hypoglycemia specifically in patients with history of CVS events. Hypoglycemia risk with SGLT2 inhibitors is minimal, specifically in case of monotherapy.

It has been believed that ketone bodies are not beneficial for human body. Like it well realized that escalated ketone bodies secondary to no insulin results in ketoacidosis. Nevertheless, it has been demonstrated that certain levels of ketone bodies have a beneficial action on the heart. Mostly SGLT2 inhibitors decrease a ratio of insulin:glucagon. On this reduction, acetyl Co A gets transformed into acetoacetate in addition to β-hydroxy butyrate in the liver. This β-hydroxy butyrate is transported to heart. This β-hydroxy butyrate gets transformed into acetoacetate in the heart, that results in escalated acetyl Co A. This escalated acetyl Co A stimulates the tricarboxylic acid (TCA) cycle along with electron-transport chain (ETC) in the mitochondria as well as ultimately escalate adenosine monophosphate (ATP) generation in the heart [64]. Moreover, escalated haematocrit by SGLT2 inhibitors aids in ATP generation by escalation of oxygen supply.

SGLT2 inhibitors possess beneficial renal protective actions

Although utilization of SGLT2 inhibitors have been done globally, lots of large scale clinical trial with regards to renoprotective actions have been performed [48,49,53-56]. Canagliflozin was demonstrated to possess promising actions on Diabetic Kidney disease. The CANVAS program had accumulated results from two trials implicating patients with T2DMwith great CVS risk. In both the trials randomization of patients with T2DM was done for receipt of canagliflozin or placebo [49]. We have already summed up on the CVS benefits, but further canagliflozin therapy demonstrated benefits on albuminuria (HR, 0.73). Besides that canagliflozin therapy was correlated with promising outcomes on the primary overall renal results (HR, 0.60) [49].

Credence trial represents one more large scale study which aimed to evaluate the actions of SGLT2 inhibitors on renal function. Here T2DM along with albuminuric chronic kidney disease (CKD) got randomized to receive canagliflozin or placebo. Enhanced glomerular filtration rate (eGFR) of every patient was 30 to < 90 ml/1,73 m^2, with all patients receiving), renin-angiotensin -aldosterone System (RAAS) inhibitors. 30% (HR, 0.70). Furthermore, these therapies decreased the rate of end stage renal disease (ESRD), doubling of serum creatinine, or renal etiology of mortality by 34% (HR, 0.68) [53]. Overall SGLT2 inhibitor canagliflozin reduced the chance of renal failure in patients with T2DM as well as CKD in a relatively small duration.

Further the actions of canagliflozin on albuminuria was documented by Fushimi., *et al*. [57], in patients with T2DM. The changes in urinary albumin excretion had a positive association with changes in systolic blood pressure (BP). Besides that, blood pressure was an independent factor for the changes in urinary albumin excretion in multivariate evaluation; with lesser the BP, the greater the improvement in albuminuria [57]. In toto canagliflozin reduced the urinary albumin excretion by reducing the BP in patients with T2DM] (Figure 4).

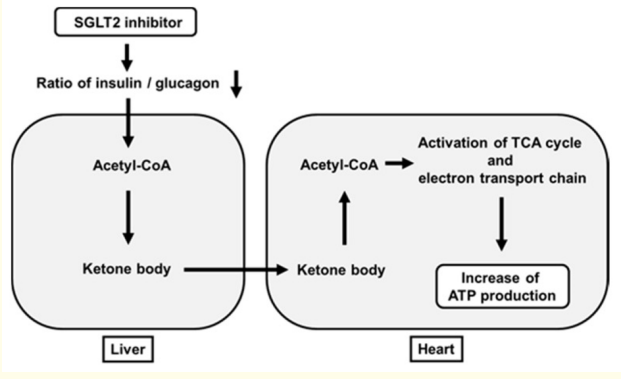

Figure 4: Courtesy ref no-21-Favorable effects of SGLT2 inhibitors on ATP production in the heart beyond their glucose-lowering effect. SGLT2 inhibitors decrease a ratio of insulin to glucagon, which leads to increased ketone bodies (acetoacetate and β-hydroxybutyrate) in the liver. Such ketone bodies are carried to the heart. After this, they activate the TCA cycle and electron transporter chain in mitochondria and finally increase ATP production in the heart.

Clear demonstration has been done lately that SGLT2 inhibitors confer protection on Kidneys, besides causing enhancement of renal results by albuminuria reduction. Different probable modes for this protection of Kidneys by SGLT2 inhibitors, that are blood pressure reduction, escalated ketone bodies generation/escalated sirtuin expression, besides constriction of the afferent arteriole via the tubule - glomerular feedback system (Figure 4).

Initially it was illustrated the single nephron GFR in Diabetic mice was greater in contrast to controls, but it was lesser subsequent to empagliflozin. *In vivo* imaging conducted by Kidokoro., *et al*. [58], documented that simultaneous afferent arteriolar dilatation in addition to escalated glomerular permeability of albumin in diabetic mice, that got mitigated subsequent to empagliflozin therapy [58]. Moreover, they demonstrated that empagliflozin

escalated urinary adenosine excretion, that resulted in hyperfiltration via afferent arteriolar constriction [24]. Moreover, ketone bodies got escalated by empagliflozin, that resulted in preservation of ATP amounts in the kidney, that aided in reduction of proteinuria in diabetic mice [59]. Moreover it was illustrated that whereas sirtuin had a significant part in different tissues in the form of an anti-ageing fact reduction of oxidative stress (OS) in addition to inflammation, it got documented that under diabetic situations, sirtuin-1 that was expressed in kidney was reduced, that resulted in propagation of diabetic nephropathy [60]. The other revelation was that canagliflozin escalated sirtuin-1 expression in the kidney of diabetic mice along with SIRT 1 expression amounts had a negative association with SGLT2 expression amounts in renal biopsy specimens of human subjects [60]. Overall SGLT2 inhibitors have a protective action on Kidney via a lot of pathways like escalated ketone bodies generation, as well as sirtuin expression, constriction of the afferent arteriole via the tubule - glomerular feedback system (Figure 5).

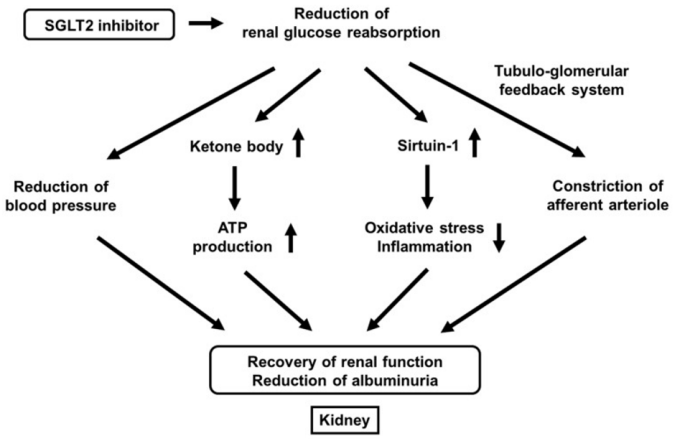

Figure 5: Courtesy ref no-21-Favorable effects of SGLT2 inhibitors on renal function beyond their glucose-lowering effect. SGLT2 inhibitors reduce renal glucose reabsorption, which leads to the reduction of blood pressure, increase of ketone bodies, increase of sirtuin-1 expression, and constriction of afferent arteriole. All of such alterations lead to the recovery or renal function and the reduction of albuminuria.

Utilization of SGLT2 inhibitors (adjuvants) in type 1 diabetes mellitus in addition to insulin preparations

Different clinical trials have utilized SGLT2 inhibitors in patients with type 1 diabetes mellitus (T1DM). Initially type 1 dapagliflozin got approval for utilization in the form of adjuvant therapy to insulin preparations in T1DM presenting with bad glycaemic regulation [61,62]. As far as Japan was concerned both ipragliflozin addition to dapagliflozin can get utilized in the form of adjuvant therapy to Insulin in T1DM patients. SGLT2 inhibitors cause a reduction of glucose as an adjuvant therapy with need for smaller daily insulin doses. Additionally, as SGLT2 inhibitors result in reduction of body weight, while insulin preparations result in escalated body weight, initiating SGLT2 inhibitors as well as reducing insulin dosage would cause a net loss of weight in addition to abrogation of insulin sensitivity. With reduction of Insulin dosage the incidence of hypoglycemia also gets reduced. Since hypoglycemia initiates a lot of clinical complications like acute coronary artery syndrome, fundus haemorrhage as well as unconscious hypoglycemia in view of absence of catecholamines liberation, hence we need to avoid hypoglycemia in clinical scenario. Additionally, as hypoglycemia results in brain damage that promotes dementia generation, it is really significant to decrease hypoglycemia risk, particularly in elderly T1DM patients. Nevertheless, due to certain problem regarding diabetic ketoacidosis secondary to SGLT2 inhibitors utilization, that has to be kept in conscience regarding risk of diabetic ketoacidosis in T1DM patients specifically.

Adverse actions of SGLT2 inhibitors-Caution while their utilization

Besides the multiple actions of SGLT2 inhibitors much way too far from anticipation, certain side effects need to be taken into account like urinary tract infection (UTI) or genital infection. Thus, it got documented that despite the actions of SGLT2 inhibitors were comparable with regards to glycaemic regulation in large scale trials, certain safety issues like repeated UTI as well as genital infections taking place. Additionally, risk of ketoacidosis existed specifically in T1DM. Renal sodium reabsorption in addition to glucose metabolism are intricately associated with acid-base balance, along with many posits have been cited for reasoning of ketoacidosis (either hyperglycemic or euglycaemic) in patients receiv-

ing SGLT2 inhibitors. In toto UTI as well as genital infections that might be occasionally severe, that can limit compliance of patients or needing hospitalization for urosepsis as well as pyelonephritis, along with the risk of ketoacidosis correlated with SGLT2 inhibitors might create confusion with regards to the treating physician.

Recently the new pandemic got stimulated by novel corona virus infectious disease (COVID19) all over the world. The mortality in COVID19 infection proved to be very high, with the main etiology of demise being pneumonia [64]. Additionally, the mortality in COVID19 along with diabetes mellitus was very high [65]. SGLT2 inhibitors might escalate the chances of COVID19-associated ketoacidosis in cases of patients with severe insulin deficiency in cases of patients with T1DM or T2DM [66]. Hence we need to keep both benefits in addition to side effects of SGLT2 inhibitors.

Conclusion

Thus, concluding that SGLT2 inhibitors in a modest, albeit significant enhancement of beta cell function in addition to beta cell glucose sensitivity. Long time studies pointed that maintenance of glucose reducing action following a minimum of 2 yr of therapy. Only limitation of the study is that no washout studies have got performed as far as we know to evaluate if enhancement of beta cell function gets maintained following omitting of SGLT2 inhibitors. As far as insulin sensitivity is concerned, various research groups have documented escalated insulin sensitivity, but the degree of enhancement was not much. It is posited that advantageous actions of SGLT2 inhibitors therapy is basically secondary to reduction in glucotoxicity. Nevertheless, clinical trials evaluating along with insulin sensitivity over longer time duration are minimal. It is possible that treatment for over3-4mths might demonstrate separate outcome. Like data point that following 3 - 4 months, energy decreases get compensated by escalated food intake which could reason out why body weight reduction doesn't occur following this period of time [67].

SGLT2 inhibitors known to cause reduction in glucose by escalating urinary glucose excretion, besides demonstrating unanticipated actions like antiobesity action. SGLT2 inhibitors possess beneficial actions on Pancreatic βcells function. They ameliorate insulin resistance in the insulin target tissues. SGLT2 inhibitors are efficacious in NAFLD therapy as well, at least partly secondary to abrogation of hyper insulinemia. In the dapagliflozin group significant body weight reduction in addition to visceral fat area decrease was observed. The liver:spleen ratio was significantly escalated by dapagliflozin or. Besides all these they further possess cardio in addition to renoprotective actions. [Already reviewed in detail in the NAFLD section]. Further they can get utilized as adjuvants to insulin in T1DM. Still one has to keep in mind the side effects of SGLT2 inhibitors in view of their mode of action of glycosuria that results in UTI along with genital infection, besides resulting in ketoacidosis. From all these one knows that SGLT2 inhibitors are wonderful antidiabetic agent that can not only ameliorate obesity, but effective in treating NAFLD associated with weight reduction, contrary to pioglitazone which achieves the same, besides being efficacious in Diabetes mellitus therapy efficaciously along with not resulting in hypoglycemia. Hypoglycemia remains one of the problems on making a decision of many other antidiabetic agents in view of it being a severe effect and can result in brain damage. Only worrying thing is its use in T1D where kit might result in ketoacidosis, that remains the only worrying problem on utilization of this drug, rest side effects like UTI, genital infections can be avoided by better hygiene etc. hence their label as magical drugs possessing multiple actions like besides it cause ng antidiabetic actions it further results in achievement of weight reduction, beneficial in NAFLD therapy, besides its proven cardioprotective and renoprotective actions in human beings and used worldwide for these actions, enhancing protection of pancreatic beta cell protection and preventing their deletion in addition to their preservation, along with their potential to be used in the most severe T2DM, besides adjuvants in T1DM that can aid in reduction of insulin dosage and hence neutralize the weight promoting actions of insulin.

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Volume 4 Issue 7 July 2021