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SGLT2 and GLP - 1 Inhibitors: Enlightening their Role beyond their Glucose Lowering Properties

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Abstract: ***Cardiovascular illnesses continue to be the top cause of death among type 2 diabetics. There have been numerous advancements for treatment of kidney disease associated with diabetes during last five years. Glucagon-like peptide-1 receptor and sodium-glucose cotransporter-2 inhibitors were originally utilised in glycaemic control, but research has demonstrated that their profits also extend to cardiac and renal outcomes. There is a high hazard of heart disease and chronic kidney disease, type 2 diabetes care today involves a increase in the medication for the control of different health issues caused by diabetes. In this paper we discuss the rationale for using SGLT2 inhibitors and GLP-1 in patients with type 2 diabetes in combination manner to preserve the heart and kidneys. SGLT-2 and GLP-1 inhibitors have diverse roles in apart from glucose lowering properties that helps to reduce the side effects. Patients with non-diabetic kidney disease may advantage from these medicines as well. Hypertension, Body weight, and inflammation are all prevalent variables for kidney disease, regardless of whether or not diabetes is present.***

Keywords: SGLT-2 inhibitors, GLP-1 inhibitors, Cardiovascular, Glucose-lowering agents

1. Introduction

Diabetes is a long-lasting illness that distresses maximum population throughout the world. Diabetes remains leading cause of renal disease, cardiovascular disease, and hypertension, among other significant complications. A succession of diabetic controlling medications has been developed and authorized to decrease glucose level throughout the last decade. For T2D patients, these medications have both cardiac and renal advantages. People with diabetes, thiazolidinediones can be the reason of fluid preservation and high peril of heart failure. The GLP-1 on the other hand, has been related to better cardiac and renal consequences in T2D patients. Because they improved cardiac and kidney outcomes in T2D patients, sodium-glucose transporter-2 (SGLT-2) inhibitors were acclaimed as beneficial therapy. These diabetes controlling medications have cardiac advantages with respect to their glucose-lowering characteristics. Proteinuria can be minimised through inflammatory therapy, as well as systemic or glomerular hemodynamic stability. Blood pressure is reduced and kidney function is preserved when GLP-1 and SGLT-2 inhibitors are used. Older glucose-lowering treatments were effective in terms of meeting glycaemic goals, but they were ineffective in terms of 'hard' kidney or cardiovascular (CV) outcomes. Significantly, previous anti-diabetic drugs such thiazolidinediones were linked to coronary disease hospitalizations, as well as hypoglycaemia and increase in weight with sulfonylureas and insulin [7]. These newer medicines have proven advantageous for CV and renal disorders, and the amalgamation of these drugs is especially intriguing due to mechanistic and clinical interaction. Sodium- glucose cotransporter-2 (SGLT2) inhibitors, such as empagliflozin, dapagliflozin, and canagliflozin, are approved for lowering blood sugar in people with T2DM, as well as reducing renovascular consequences and promoting weight loss. SGLT2 inhibitors work by preventing glucose and salt absorption in the early proximal renal tubule, consequential in increased excretion of glucose in the urine and lower glucose levels. The enhancement of sodium excretion in urine, which results in osmotic diuresis and lower blood pressure, is another advantage of SGLT2 inhibitors. Albuminuria is the renal protective mechanisms of SGLT2 inhibitors, as it lowers intraglomerular pressure and protects tubular cell injury. These pleiotropic effects have resulted in a reduction in cardiovascular events as well as the preservation of renal function.

Mechanism of SGLT2 Inhibitors

They improve glucose level through two methods. Foremost, by dropping the levels for reabsorption of glucose and the verge for glycosuria, resulting in glycosuria. Additional, by minimising glucotoxicity (due to a decrease in the level of plasma concentration of glucose due to glycosuria) and improving functions of β Cell in peripheral tissues, that leads to upgrade sensitivity of insulin in peripheral tissues. A rise in endogenic production of glucose, probably due to an upgradation of levels of glucagon concentrations in the plasma, partially offsets these beneficial metabolic alterations. As their method is autonomous of insulin secretion, they have a little risk of hypoglycaemia thus be additional to any contextual therapy plan which help to lower the glucose level. When used with a sulphonyl urea or insulin therapy, they may produce hypoglycaemia.

Direct Physiologigal Effect of SGLT2 Inhibitors

Glucose controller has Improved Glucosuria caused by the inhibition of the SGLT2 transporter. Gliflozins prevent reabsorption of glucose in the different segments of proximal tubule by blocking the SGLT2 cotransporter. TmaxG is reduced to roughly 40– 80 mg/dL, and the renal threshold for glucosuria is decreased. To compensate for the considerable energy loss caused by glucosuria, SLGT1 cotransporters boost reabsorption to 40%. [14]. Dual SGLT2- knockout mice exhibit considerably more glucosuria than solo SGLT2-knockout mice, according to a preclinical investigation in rats. Furthermore, SGLT2 inhibitor do not augmented peril of hypoglycaemia. A 0.5–1% reduction in HbA1c indicates improved glucose control. This results in improved insulin sensitivity and beta-cell

function, which is important character of SGLT2 inhibitor in controlling diabetes. In SGLT2 inhibitor investigational studies have shown a consistent effect in glucose management.

Secondary Roles of SGLT2 Inhibitors

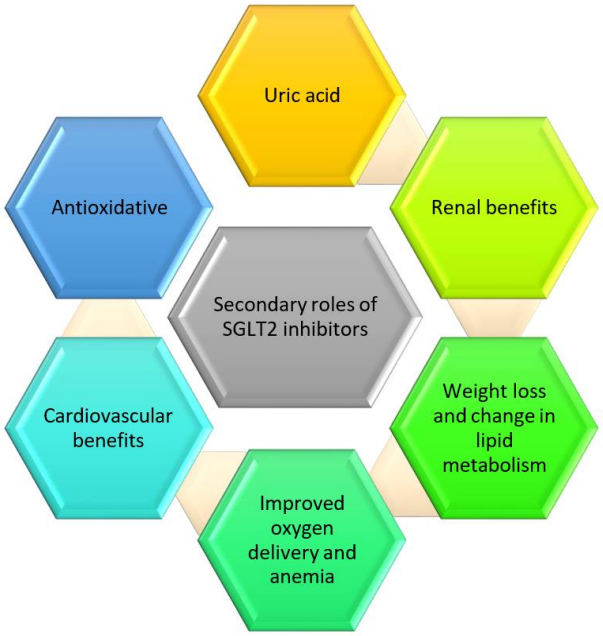

Figure 1: Secondary roles of SGLT2

Weight Loss

After 6–12 months of treatment with SGLT2 inhibitors, patients lose between 2 and 4 kg. The first weight loss is due to volume constriction, which is followed by caloric squandering due to glucosuria. During the treatment when reduction in weight is required, ADA guidelines propose SGLT2 inhibitors as the first anti-diabetic medicine. Inhibition of SGLT2 and the resulting glucosuria results in a condition of deficiency of glucose, fluctuating energy substrate utilisation in fats. It lowers cellular lipotoxicity while also reducing oxidative stress. This promotes the formation of ketone, which appears to be active substratum for nephron and cardiac cells.

Improve in Albuminuria

SGLT2 inhibitors has shown dramatically albuminuria declination in patients with or without diabetes along with renal impairment in clinical trials. This impact is both independent and additional to the RAAS inhibition effect. Serum creatinine improvement is complex, with afferent arteriole vasoconstriction, a drop in intraglomerular pressure and hyperfiltration, and blood pressure elevation all contributing. Various investigations have also revealed that because SGLT2 cotransporters consists of podocytes, SGLT2 inhibition improves them, and that dapagliflozin or empagliflozin minimizes effacement by lowering blood sugar and podocyte dysfunction with decreasing glucotoxicity. Albuminuria would enhance the chances of this.

Improved Oxygen Delivery

The reduction in energy expenditure and enhancement in proximal tubular cell mechanism lowers demand of oxygen and raises oxygen tension of corticoid. The SGLT1 cotransporters resorb glucose delivered to the latter section of the proximal tubule, enhancing energy along with consumption of oxygen in the outer medulla of kidney. The HIF1 and HIF2[24], as well as the release of erythropoietin, are stimulated when oxygen availability is reduced [25]. This, combined with a moderate volume contraction, raises haemoglobin levels and improves oxygen delivery to various tissues. Haemoglobin levels in patients treated with SGLT2i have improved in clinical trials. Dapagliflozin appears to aid enhance erythropoiesis by suppressing h iron-metabolism related proteins.

Uric Acid

It is a by-product of purine nucleotide breakdown that are linked with heart and circulatory disorders. Surprisingly, uric acid has been linked to aggravates oxidative stress along with the inflammation, also leads to the bioavailability reduction and hence dysfunction of endothelial. Furthermore, uric acid has been demonstrated to stimulate the renin- angiotensin-aldosterone pathway. According to a analysis of 62 SGLT2i RCT studies, SGLT2i has strong evidence of lowering uric acid in people with T2DM. Patients with chronic renal disease (eGFR) had an effect that lasted even after long-term treatment.

Blood Pressure Reduction

With SGLT2 inhibitors, they are useful in falls BP, which are comparable throughout the class. SGLT2 inhibition causes natriuresis and osmotic diuresis, as well as a ECF contraction and plasma volume contraction, due to the connector of sodium reabsorption and glucose in the proximal tubule. These blood pressure reducing effects may also be seen in people who do not have T2D. Almost certainly, mechanisms like lipotoxicity and oxidative stress, subsidize to the pathophysiology of cardio and renal diseases in Type 2 diabetes.

Cardiovascular Properties

The decrease in cardiac related fatalities who are receiving SGLT2 inhibitors began initial in the EMPA-REG trial, therefore it's doubtful that its participation in atherogenesis was the main mechanism by which it attained this improvement in shorter period of times. It effects on plasma volume is perhaps a better explanation. However, because the reductions in cardiovascular death persisted throughout the study, it's intolerable to rule out the possibility of other effects for the longer duration, such as atherogenesis, myocardial, and ventricular remodelling, all of which have been linked to increased cardiovascular mortality. Changes in plasma volume markers were the significant mediators in lowering mortality rate from cardiovascular disorders, rise in haematocrit (haemoglobin) levels act as essential role. Added research revealed that despite taking different dosages of empagliflozin (10mg and 25mg), both dosage groups saw the same cardiovascular benefits. The effects of empagliflozin on people with cardio disorders associated with (EMPA-HEART) study of diabetes, a randomised study in which empagliflozin affecting people with type 2 diabetes mellitus and s arteria coronaria disease, with a substantial heart failure, established a noteworthy in left ventricular mass index reduction over period of 6 months [33]. It's also worth noting that the effect on ventricular mass in this study

had nothing to do with blood pressure, autonomic changes and preload. It reveals a distinct effect on the myocardium, which could be important in the treatment of other heart disorders such ischemic heart disease and cardiomyopathies [34]. Atherogenesis is a term used to describe the progression of atherosclerosis. In research it was investigated the consequence of tofogliflozin as a course of atherosclerosis in order to better understand the drug's involvement in the atherosclerotic pathway. Carotid atherosclerosis was measured using carotid intima-media viscosity in prospective randomised research in which patients with Type 2 diabetes with no evident Cardiovascular history were given tofogliflozin or placebo. Between the two groups, there was a rise in HDL-c but little difference in carotid [35]. Apart from the absence of evidence linking carotid to atherosclerosis, analysis found there was no link between the two of them. [35] Type 2 diabetes mellitus patients and a background of heart disease who are on empagliflozin had a 48 percent reduction in mortality rate, a 43 percent reduction in death rate, and a 50 percent declination in heart failure hospitalisation in a double-blinded randomised controlled study published in 2019 [36]. Mortality due to cardiovascular reasons or hospitalisation for heart failure occurred in 444 of 5499 (8.1%) and 250 of 2747 (9.1%) of patients already on ertugliflozin compared to placebo [37].

Renal Effects

The mechanisms by which SGLT2 inhibitors protect the kidneys is still developing [38]. Although adequate level of glucose is essential for decreasing the chances kidney disease associated with diabetes, metabolic effects such as glucose reduction, better insulin sensitivity, and reduced glucose toxicity are beneficial, the other key modes of act beyond the glucose lowering properties. These include straight natriuretic effects of inhibition of SGLT2 on the renal function, such as glomerular haemodynamic normalisation via tubuloglomerular feedback restoration, and improved renal energy efficiency. Despite these other related benefits, like blood pressure and body weight decreases.

Antioxidant

Hypoglycaemic medicines that target SGLT2 generating glycosuria are known as SGLT2 inhibitors (SGLT2i). As a result, SGLT2 improves insulin resistance in diabetes by lowering the levels of glucose in an independent of insulin manner [39,40]. Mitochondrial dysfunction is a symptom of DKD. The SGLT2 is responsible for glucose and sodium uptake and is found in the membrane of apical in the kidney. Overactivation of SGLT2 in diabetic individuals disrupts glucose and salt homeostasis, affecting mitochondrial function at several levels; fission and fusion imbalances, as well as mitochondrial fragmentation. Physiology of the oxidative phosphorylation chain from the induction of oxidative stress, leading to depletion of ATP, a metabolic shift to oxygen-independent energy sources. Damaging of DNA of mitochondria, causing mtDNA reduction copy number and an increment in mtDNA release into the cytosol, NLR family pyrin domain-containing 3 inflammasome activation, and into the extracellular space, triggering immune cell recruitment and the inflammatory response.

Glucagon-Like Peptide-1

Intestinal endocrine cells secrete GLP-1 in retort to nutrition consumption, which helps pancreatic -cells secrete insulin. GLP-1 works by requisite to GLP-1 and then activation adenylate cyclase, that results in the production of cAMP. In pancreatic -cells, cAMP increases insulin production by PKA activation and exchange factor directly activated by cAMP 2 [41]. GLP-1 lowers blood sugar through stimulating glucose-dependent insulin release from pancreatic islet cells, which slows emptying time of gastric and leads to appetite stimulation reduction in the brain. This is the mechanism by which GLP-1 can lower blood sugar and help people lose weight [42,43]. GLP-1 is found in variety of organs besides the pancreas, including the intestines, kidneys, heart, and central nervous system [43]. As a result, GLP-1 agonists can protect many organs in the body, including the cardiovascular system, the lungs, and the kidneys [44]. GLP-1's positive effects in cardiac system, such as BP regulation as well as improved function of endothelial, can also assistance to preserve the kidney. GLP-1, in particular, exhibit anti-apoptotic and anti-inflammatory properties, as well as the ability to boost nitric oxide synthesis [45].

Kidney Injury

The most common cause of hospital-acquired AKI, contrast-induced nephropathy, includes numerous pathophysiological pathways, including oxidative stress, dysfunction of endothelial and renal hypoxia [46]. In a rat model, Hussein et al. found that exendin-4, a GLP-1R agonist, had a preventive effect against contrast-induced nephropathy. Exendin-4 pre-treatment improved renal function, oxidative stress, vascular dysfunction, and apoptosis biomarkers [47]. A rat model of renal ischemia/reperfusion damage produced similar results. The kidney injury in rats pre-treated with exendin-4 before reperfusion was reduced by reducing caspase-3 expression and macrophage infiltration while boosting heme oxygenase-1 (HO-1) expression [48]. In mice, exendin-4 decreased cisplatin-induced kidney damage and apoptosis [58]. Chronic Kidney Disease (CKD) is a disease that affects the kidneys. In non-diabetic CKD, there are few data on the usage of GLP-1R agonists. In a mouse model of T cell–mediated glomerulonephritis, a GLP-1R agonist (liraglutide) was demonstrated to have anti- inflammatory properties [49].

Hypertension:

Clinical manifestations from the LEAD series of studies showed that 26 weeks of liraglutide treatment can lower SBP [50]. Exenatide improved T2DM patients' blood pressure and blood total cholesterol for seven years in a DURATION open-extension study [51]. Dulaglutide steadily shows improvement in blood pressure and cholesterol levels in participants in the REWIND and AWARD5 studies [52]. GLP-1 lowers blood pressure by acting as a diuretic which also have other effects on the kidneys [53]. GLP-1 also enhance the sensitivity of insulin, which minimizes problem of hypertension in T2DM, by lowering angiotensin II levels. [54,55]

Antiapoptotic and Antifibrotic Effects

It alleviate Diabetes associated within kidney impairment by reducing cell death of kidney and fibrosis, both of which elevated in long-lasting hyperglycaemia.[56,57] In addition to

other found that the DPP-4i reduced kidney tissue injury induced by diabetes in human endothelial cells via suppressing apoptotic pathways.[58] Furthermore, Tews revealed in year 2009 that exendin-4 reduced cytokine-induced tissue injury in pancreatic beta cells by blocking apoptotic pathways.[59] In addition, many other researchers discovered in 2014 that GLP-1 via sitagliptin reduced apoptotic cell death and enhanced kidney function in diabetic rats.[60]

Cardiovascular Effects

Glucose levels, dyslipidemia, weight of body, and BP are different factors that can be the main cause heart related disease associated in T2DM patients. During various studies it seems that most GLP-1 enhance the measures and so slow the evolution of atherosclerosis, especially with regard to LDL-C levels.[63] A randomised study published in 2015 found that taspoglutide can lower cholesterol level, LDL cholesterol, and triglycerides [61]. The combination of liraglutide and metformin reduced C-reactive protein in atherosclerosis and LDL in new-onset diabetic patients undergoing standard statin therapy.[62] Liraglutide (1.2 mg/d) alone was found to be highly beneficial on lipid metabolism and cardiovascular health than liraglutide with metformin or metformin alone in studies with comparable glycaemic control.[63]

2. Conclusion

GLP-1 and SGLT-2 inhibitors that lower sugar levels may have non-diabetic indications. Although the positive benefits of GLP-1 and SGLT2 on kidney role has described in many researches, clinical evidence is necessary. SGLT-2 are showing suitable as a kidney disease treatment without diabetes. It has the ability to reverse both systemic and glomerular
hemodynamic changes, resulting in cardiorenal protection. SGLT2 inhibitors have been found to reduce kidney and cardiovascular problems. Non-diabetic indications may exist for GLP-1 and SGLT-2 inhibitors that lower sugar levels. Different studies have showed that all of these anti-diabetic medicines have other actions in addition to glucose reduction. Although several investigations have proved the favourable effects of GLP-1 and SGLT2 inhibitors, clinical data is still required. kidney disease not associated with diabetes treatment with SGLT-2 inhibitors is looking promising. They have the ability to preserve the cardiorenal system by reversing both systemic and glomerular hemodynamic abnormalities.

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