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Review Article

Combination Therapy of SGLT 2 Inhibitors and GLP 1 Receptor Agonists for Glycaemic Management through Weight Reduction

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Abstract

A great deal of anti-diabetic drugs leads to weight gain, which could contribute to obesity and possibly both diabetes and obesity. Glucose-lowering medications that contain sodium-glucose co-transporter 2 (SGLT2) inhibitors work by preventing the kidneys from reabsorbing glucose and sodium, which causes glycosuria and lowers plasma glucose levels. Consequently, its effects include decreases in HbA1c, blood glucose levels, and blood pressure along with decline in body weight and adiposity. Consistently, people on medications that inhibit SGLT2 tend to lose weight, but this weight loss is only modest since opposing regulatory processes work to keep the body's weight constant. This has driven researchers to investigate the use of SGLT2 inhibitors in combination with other drugs that work by reducing appetite, such as glucagon-like peptide 1 receptor agonists (GLP1RAs). In a retrospective study at the Wolver Hampton Diabetes Centre, researchers evaluated the effectiveness of combination therapy using GLP-1 agonists and SGLT-2 inhibitors in the management of diabetes and obesity. Patients on the combined regimen showed statistically significant improvements in clinical measures like body weight reduction, glycated hemoglobin (HbA1c) reduction, lower BMI, and reduced insulin dose. Such combinations, which include SGLT2 inhibitors, are intriguing because of the bodyweight effects and the indications of protection of cardiovascular and renal problems. These results imply that combination therapy using GLP-1 agonists and SGLT-2 inhibitors offers individuals with diabetes and obesity a promising treatment choice

Keywords: Diabetes Mellitus, obesity, SGLT 2 inhibitors, GLP 1 receptor agonist.

Introduction

Diabetes mellitus (DM) refers to a group of metabolic illnesses characterized by chronic hyperglycemia leading to vascular complications[1]. In the context of cell dysfunction, insulin resistance, or both, diabetes is a long-term metabolic disorder characterized by higher blood glucose levels that come from absolute or relative insulin shortage. Hyperglycemia, the last common route on which many metabolic derangements converge, is the sole diagnostic criterion used to classify diabetes as a set of illnesses rather than as a single disease.[2] The old and confounding criteria of Diabetes classification as insulin-dependent (IDDM) or non-insulin dependent (NIDDM) proposed by WHO in 1980 and 1985 are no more used and the new system of classification defines diabetes as four types: Type 1, Type 2, "other specific types," and gestational diabetes (GDM) [3].

Type 1 DM is autoimmune disease caused by insulin deficiency as a result of death of pancreatic islet –cells[4]. In type 1, there is loss in beta-cell mass and significant insulin depletion characterized by the loss of the pancreatic islets of beta cells and complete insulinopenia.[5] Although, T1DM was once thought to develop mostly during childhood or adolescence, but it is now recognized that it can be developed throughout life, even in people who are over 80 years old [6].

Type 2 diabetes mellitus (T2DM), which can either be due to decreased insulin production, insulin resistance, or both. The root cause primarily being imbalance in carbohydrate, lipid, and protein metabolism[7]. People who have T2DM are more susceptible to multiple short- and long-term complications, which frequently results in an early death. Due to rapid increase in prevalence, insidious start, and late identification, individuals with T2 DM are likely to have greater morbidity and death.[8]

Gestational diabetes mellitus (GDM), is a frequent metabolic issue during pregnancy, which is linked to a higher risk of unfavorable pregnancy outcomes for both women and their offspring.[9] The most important GDM risk factor is having overweight or obesity prior to conception.

Besides these common three types, the congenital diabetes, maturity-onset diabetes of the young (MODY),

and numerous diabetes-associated syndromes are merely a few of the clinical disorders that are often characterized by early-onset diabetes and are included in monogenic diabetes. Given that the majority of MODY cases have a genetic cause, the upsurge in prevalence of overweight and obesity has also been one of the major risk for DM [10].

Understanding Diabetes mellitus and Obesity

Excessive weight gain may appear like an obvious obesity repercussion but progressively gaining weight is the catalyst for developing future metabolic diseases, of which T2DM is unquestionably linked to obesity. The result of metabolism-related T2DM is quite straightforward: hyperglycemia caused by decreased insulin sensitivity due to the loss of functional b-cell mass. Obesity is a key factor in the development and progression of this condition. Genetic and epigenetic vulnerability, changes in the microenvironment that impair insulin signaling, and deteriorated beta-cell function also influence obesity and DM. Fig 1 depicts genetic and environmental factors influencing obesity and thus islet function and T2DM [11].

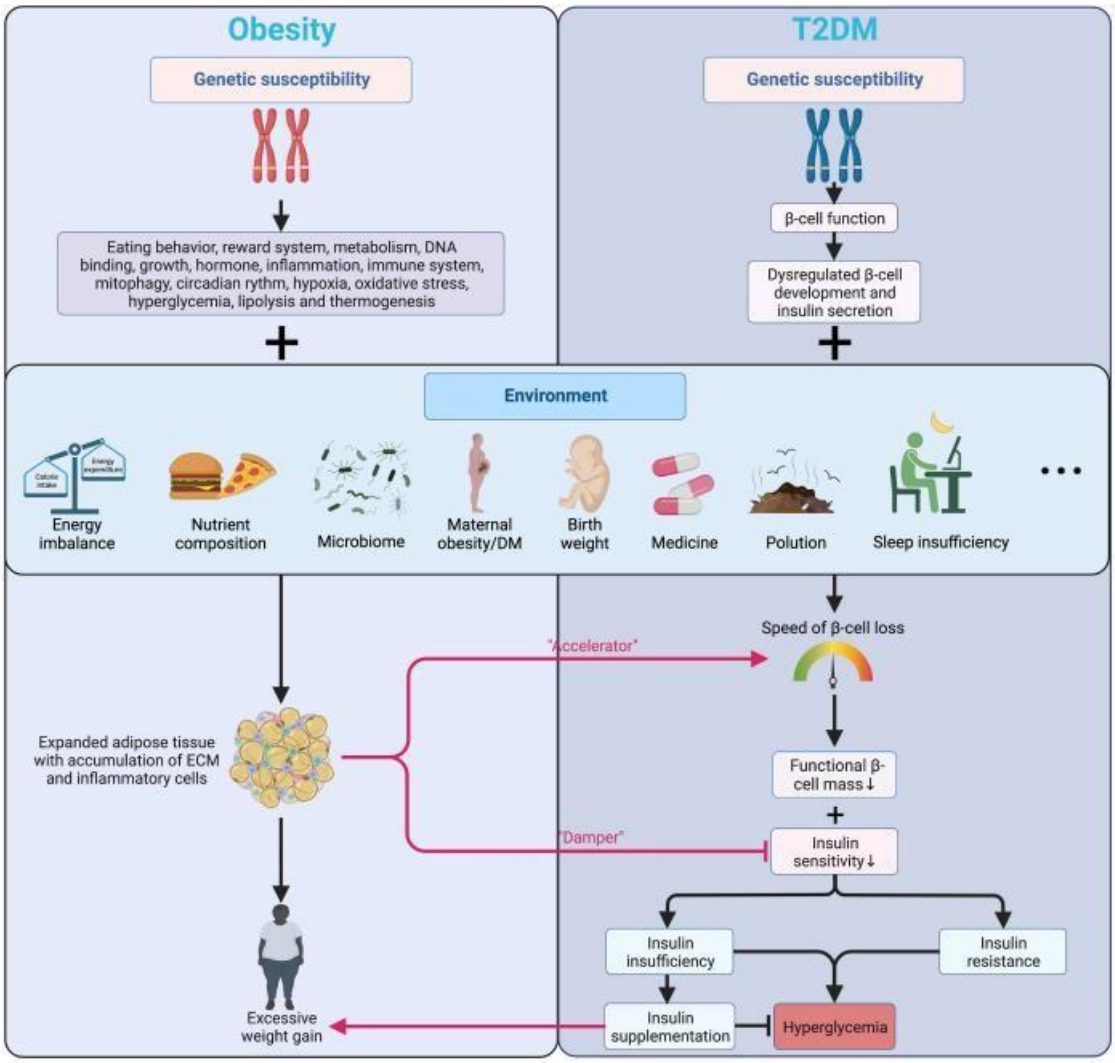


Figure 1: Genetic and environmental factors influencing obesity and thus islet function and T2DM

Obesity has a significant effect on tissue insulin sensitivity, which in turn affects the systemic glucose homoeostasis. Weight loss is critically important to prevent such ectopic fat deposition. Studies have revealed that every 1 kg weight loss was associated with a 16% relative risk reduction in individuals progressing from impaired glucose tolerance to T2DM [12]. Individuals with a body mass index (BMI) of 30–34.9 kg m^2 have a hazard ratio for more than 40% mortality it rises to 100% at a BMI of >40 kg m^2 [13]. Obesity is frequently accompanied by an increase in beta cell mass that includes hypertrophy and hyperplasia, lending support to the idea that this is an adaptation to handle the increased demand for insulin. The beta cells are still abundant in insulin granules at this point, indicating that the acute part of the stimuli secretion mechanism is insufficient [14].

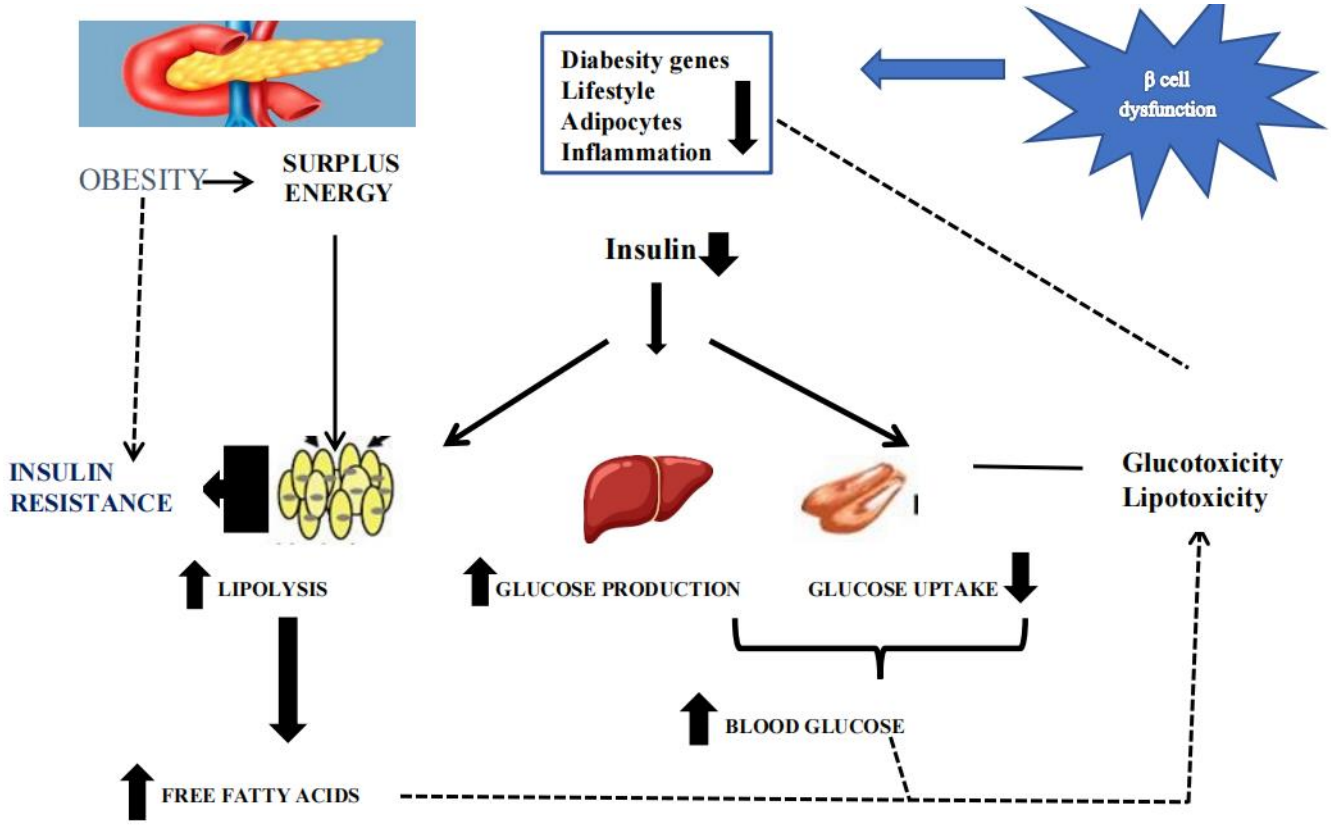


Figure 2: Influence of Obesity on Insulin Dysfunction

Combination of SGLT-2 and GLP-1 Inhibitors in T2DM

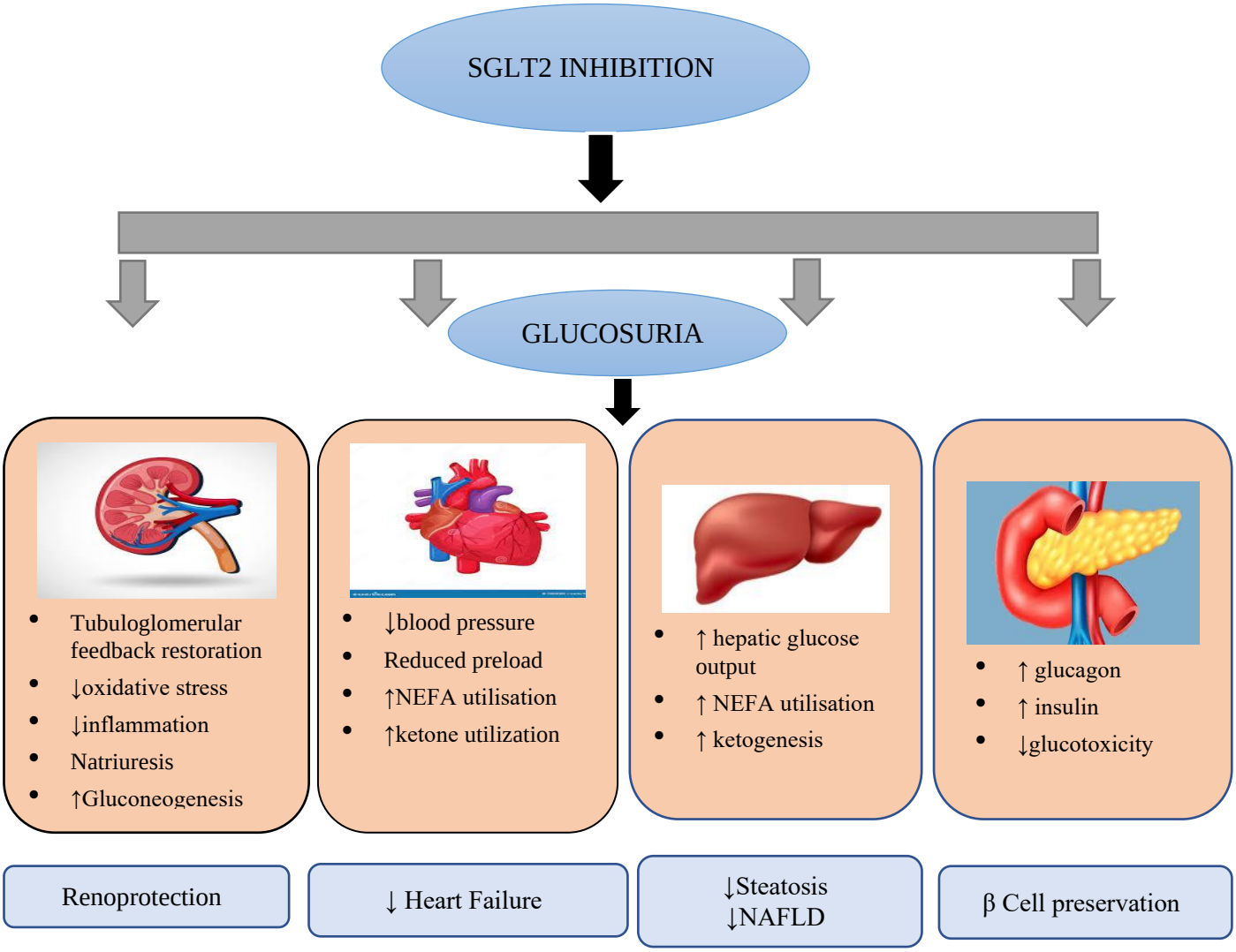
There are several oral hypoglycemic agents (OHA) which are effective in management of DM. Selective sodium-glucose co-transporter 2 (SGLT2) inhibitors are once such OHA which targets both obesity and DM. SGLT2 provide an insulin independent strategy for lowering blood glucose levels. By preventing the reabsorption of glucose from urine in the proximal tubule of the kidney, they encourage urinary glucose excretion. SGLT2 inhibitors directly reduce body weight by causing the kidneys to excrete glucose. About 60-100 g of glucose can be eliminated from the body each day in the urine as a result of SGLT2 inhibition.[15] Active co-transporters known as SGLT exist in the brush border of the S2 and S3 segments of the proximal renal tubules. It functions by inhibiting the excretion of the filtrated urine glucose and reabsorbing it. Lipids, which make up cell membranes, prevent the absorption of polar substances like glucose. To achieve this, a glucose transporter in the form of a carrier protein facilitates the movement of glucose. SGLT2 and SGLT1 help the kidneys move glucose around more easily. Both the combined absorption of sodium across the luminal membrane and the active transport of glucose across concentration gradients are mediated by SGLT2. Na^+K^+ATPase in the basolateral membrane keeps the sodium concentration inside the cell constant. The glucose transporter type 2 (GLUT2) located on the basolateral membrane allows glucose within the cell to passively diffuse into the bloodstream along the concentration gradient. 90% of reabsorbed glucose is handled by SGLT2, with SGLT1 handling the remaining 10%. While SGLT2 is found in the kidney, SGLT1 is mostly found in the small intestine. Particularly targeting these active co-transporters, SGLT2-inhibitors cause glucose to be excreted in the urine, which helps in lowering blood glucose levels.[16]

The outcomes of inhibiting SGLT:

Typically, there is no glucosuria due to filtration of glucose through the glomeruli in kidneys owing to the glucose reabsorption that takes place in the proximal tubule. The effect of SGLT inhibition leads to the formation of significant glucosuria, often between 70 and 80 g/d at therapeutic levels. SGLT2I are extremely specific inhibitors of renal glucose reabsorption. The renal tubules also contain SGLT1, which in healthy individuals likely accounts for 10% of glucose transport (it has a higher affinity for glucose but a lower transport capacity, is less selective, and may transport galactose) [17].

GI tract glucose transport and SGLT1 function:

The primary glucose transporter responsible for mediating glucose transfer in the GI tract is SGLT1. It is necessary for adequate glucose and galactose absorption. Due to severe diarrhea, glucose-galactose malabsorption is a disorder caused by genetic abnormalities in the SGLT1.



NEFA: Non esterified fatty acids

Figure 3: shows effect of SGLT Inhibition on different organs

While the Central Nervous System (CNS) contains SGLT2 proteins, little is known about how SGLT2 inhibitor affects cognitive deficits. Fig 3 shows effect of SGLT Inhibition on different organs. Preclinical research has shown that SGLT2 inhibitor improves cognitive impairment in T2DM and obese mice by decreasing neuro-inflammation and oxidative stress while enhancing neural plasticity and the mitochondrial brain system. This helps in preventing the development or progression of neurodegenerative disorders.[18]

Role Of GLP 1 Receptor Agonists

GLP1, an endogenous incretin hormone, is generated in the small intestine's L-cells of the enter endocrine system in response to food consumption. It increases the production of insulin while suppressing the secretion of glucagon. Additionally, the CNS produces glucagon-like peptide 1. GLP1, which acts as a neuropeptide rather than a hormone, modulates food and water intake, promotes satiety, and may also regulate blood pressure and heart rate. It is released into the brain's hypothalamic nuclei by nerve endings that originate in the nucleus of the solitary tract, area postrema, and caudal brainstem. The intestinal L-cells produce GLP1, which is then absorbed by the lamina propria capillaries in the gut. Here, it can interact with the no dose ganglion's afferent sensory nerve ends, triggering neurons in the solitary tract and ultimately the hypothalamus. GLP1-receptor (GLP1-R)-mediated regulation of food intake and reward has been shown to occur lately in the lateral parabrachial nucleus Glucagon-like peptide 1 works by attaching itself to GLP1-R, a G protein-coupled receptor associated with elevated second messenger pathway activity involving cyclic adenosine monophosphate (cAMP). The brainstem, cerebral cortex, substantia nigra, hypothalamus, hippocampus, and thalamus are among the regions with glucagon-like peptide 1 receptors. Activation of these receptors is linked to improved learning, reduced oxidative stress-induced apoptosis, and increased cellular plasticity [19]. Glucagon-like peptide 1 receptor agonists (GLP-1RAs), such as liraglutide and semaglutide, were initially created to treat type 2 diabetes, but it was discovered that they were also effective in lowering blood sugar levels and body weight. GLP-1RAs reduce body weight in a variety of ways, including by reducing hunger and appetite and increasing satiety, which leads to less energy intake. [20] In

the distal ileum, GLP-1 is directly released by L-cells in response to food intake. However, the dipeptidyl peptidase-4 (DPP-4) enzyme inactivates GLP-1 within two to three minutes.41 Patients with T2DM produce less GLP-1.[21]

Studies on people with T2DM significantly revealed that well-preserved insulinotropic activity of GLP-1 was associated by a temporary reduction in plasma glucose in the usual fasting range in patients who previously demonstrated chronic hyperglycemia. [22.] Several GLP-1 RAs have been found to be effective and safe in individuals with T2DM and CKD. Trials, despite the fact that they were not developed for weight loss. Currently, the FDA has authorized only liraglutide at a higher dose for weight reduction. In a randomized controlled trial of 2254 people with pre-diabetes, liraglutide 3.0 mg daily was shown to be more effective than placebo in terms of weight loss (-6.1% vs. -1.9%) and reduced risk of diabetes (2% vs. 6%).[23]

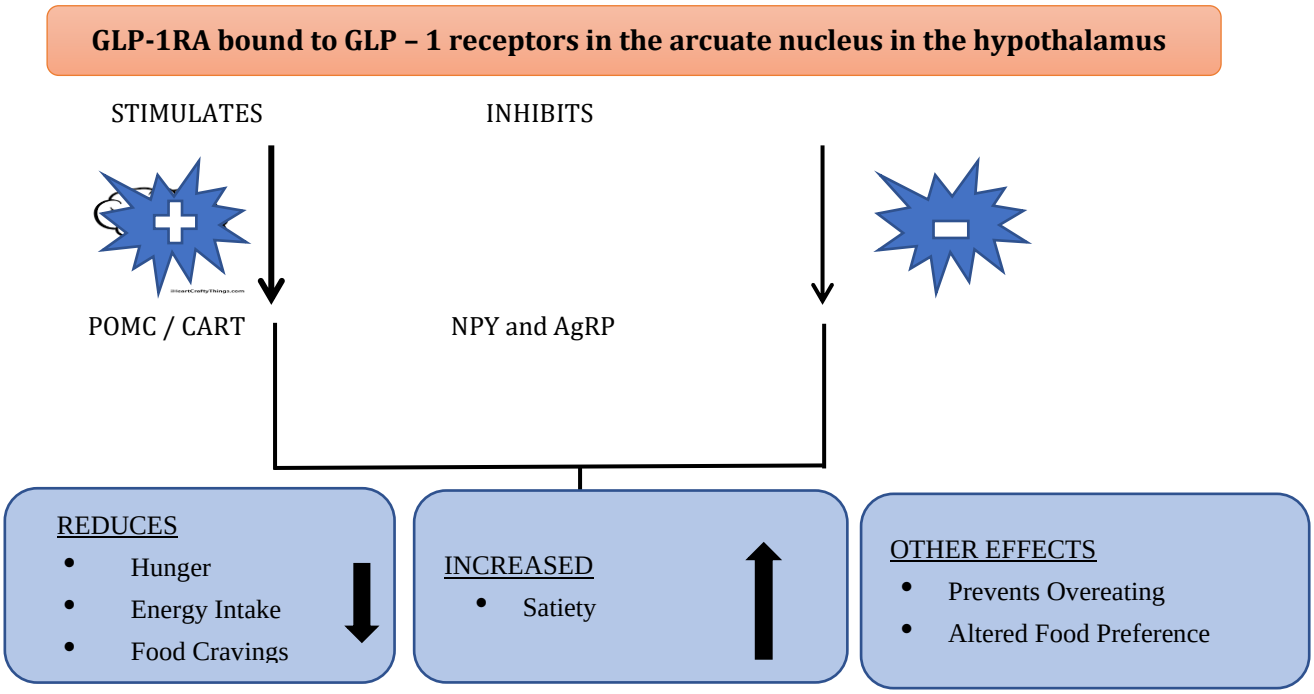


Figure 4: Role Of GLP 1 Receptor Agonists

Both GLP-1RAs and SGLT2is promote sustained weight loss through various mechanisms. GLP-1RAs also delay stomach emptying and have immediate implications on the neurological system to reduce appetite and aid in weight loss. Due to osmotic diuresis, SGLT2is reduces body water, which leads to weight loss, and it additionally allows more calories to be excreted in the urine. [24]

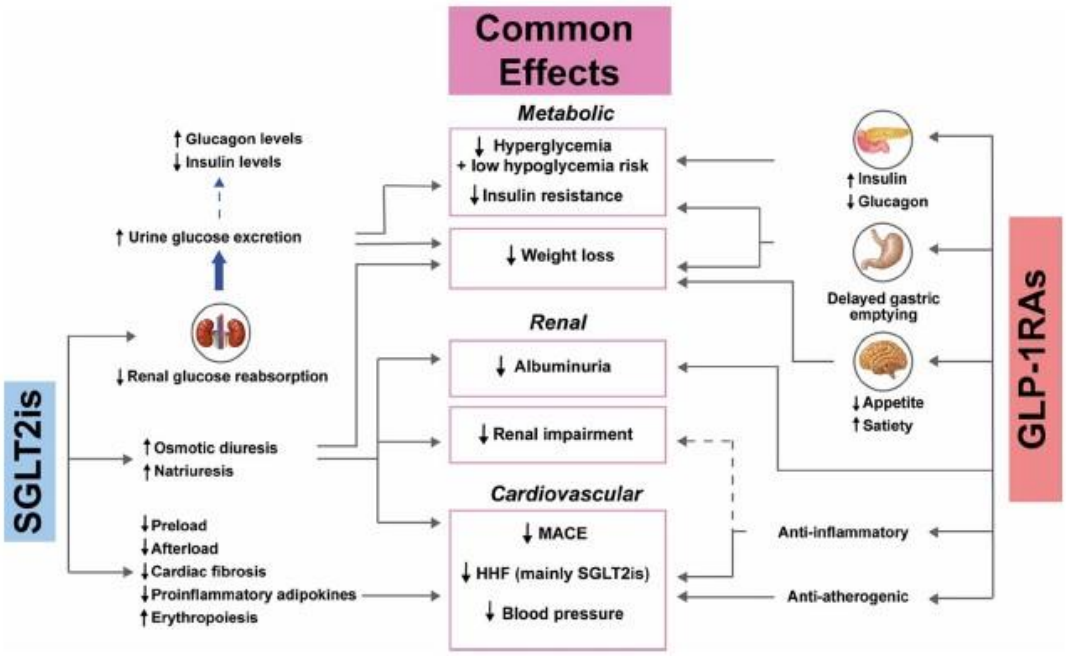
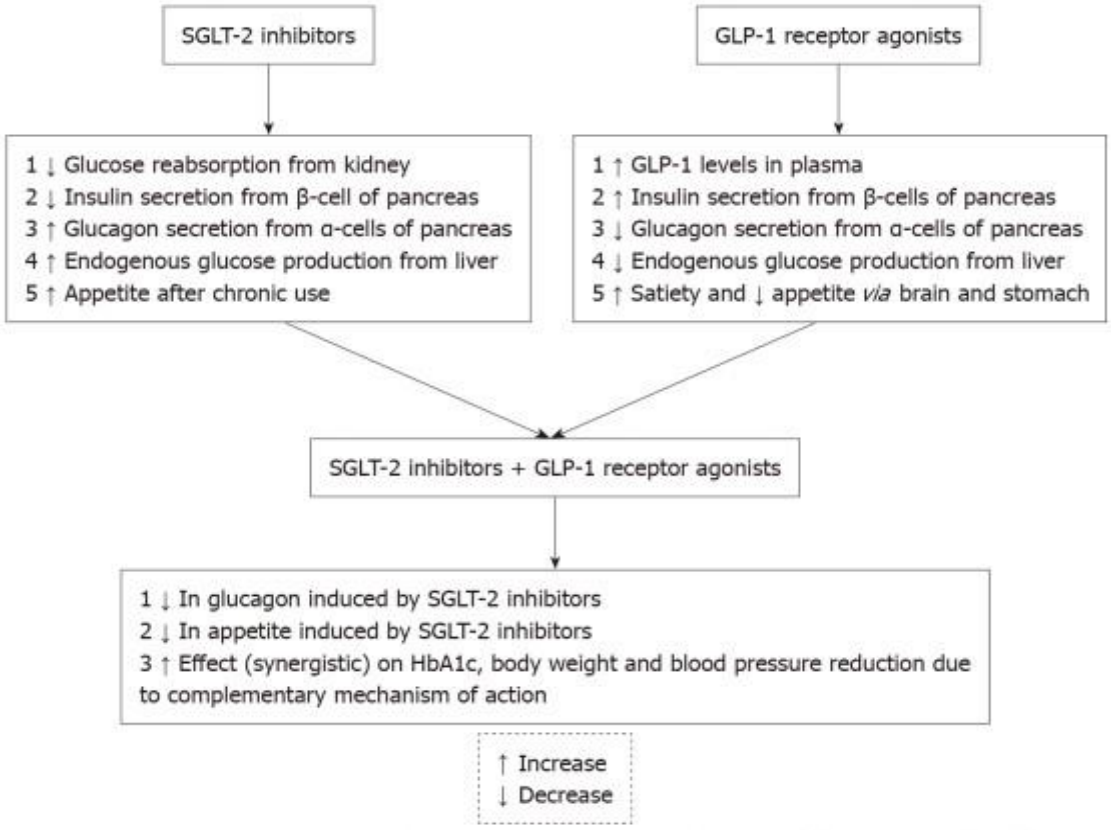


Figure 5: describes the common effects of SGLT2is and GLP-1RAs on cardio-renal metabolic syndrome

In addition to regulation of blood sugar, blood pressure, and body weight, SGLT2 inhibitors and GLP-1 receptor agonists may potentially work in combination to slow the development and worsening of diabetic nephropathy. Fig 5 describes the common effects of SGLT2is and GLP-1RAs on cardio-renal metabolic syndrome. Furthermore, they lower the incidence of many clinically significant adverse cardiovascular events, increasing the possibility that combination therapy could result in broader benefits than either medicine used alone. [25] These medications result in considerable cardio metabolic enhancements, an increase in insulin sensitivity besides reduction in cardiac and skeletal muscle fat. With decrease in hepatic fat, there is increased hepatic sensitization to insulin and reduced hepatic glucose generation. Additionally, with less beta cell fat, beta cell death is slowed, which boosts insulin secretion. [26]

Combination Medication in the Treatment of T2DM

The "Ominous Octet" of pathophysiologic abnormalities in T2DM, which consists of seven of them, may be corrected by combining GLP-1RA and SGLT-2I. By increasing insulin secretion and decreasing glucagon secretion via -cells and -cells in the pancreas, respectively, in a glucose-dependent manner, GLP-1RA reduce plasma glucose concentration. By causing glycosuria, SGLT-2I lower plasma glucose levels. This remuneration and "paradoxical" increase in endogenous glucose production (EGP) is followed by a significant rise in plasma glucagon and a decline in the fasting plasma insulin concentration.[27]



Ultimately, both the class of drug support weight loss. Weight reduction caused by GLP1RA can range from 0.2 to 7.2 kg, and 50% of patients experience weight loss of less than 5% while under treatment. With combined fluid and adipose tissue loss, SGLT2 inhibitors cause a modest weight loss of 2-3 kg. [28.]

Conclusion

Guidelines recommend at least modest weight loss, with the administration of drug therapy indicated for people with comorbidities risk factors. Weight loss is crucial in the care of people with T2D who are overweight or obese. Importantly, it is now widely acknowledged that the aim of T2D treatment should not just be maintaining glucose levels and weight loss, but rather need to be focused on continuing improvements in long-term effects, organ protection, and prolonging the years of quality-of-life advantages that accompany such improvements. It is shown that the alteration of catabolism that happens with SGLT2 inhibitors appears to influence other aspects of metabolism, which include lipolysis and ketogenesis in the liver, may eventually have impact on other organ systems and can help organ protection and long-term cardio-renal advantages. We further suggest that in future GLP-1glucagon dual agonist trials, these metabolic processes will be critical for organ protection. The mechanism of action of these interventions has the ability to maintain the body in a catabolic or exercise-like state for longer periods of time. As a result, the complimentary mechanism of action associated with an SGLT2 inhibitor and a GLP1-RA may present an alluring method for treating obesity.

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