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Stronger Together: How GLP-1 RAs and SGLT-2 Inhibitors Revolutionize Type 2 Diabetes Treatment

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Abstract

Introduction: Type 2 diabetes affects approximately 462 million people worldwide. The condition is associated with complex pathophysiology that leads to impaired glucose regulation and the development of both macrovascular and microvascular complications. The economic burden is significant, with high treatment costs and lost productivity due to complications and premature mortality. Current guidelines recommend using glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose cotransporter-2 (SGLT-2) inhibitors in combination for patients at high risk for cardiovascular disease or chronic kidney disease. These treatments have been shown in multiple meta-analyses to reduce the risk of major cardiovascular events, mortality, myocardial infarction, renal failure, and severe hyperglycaemia.

Purpose: This review examines the impact of combining GLP-1 receptor agonists and SGLT-2 inhibitors in patients with type 2 diabetes, with a particular focus on cardiovascular risk.

Materials and methods: The review analyzed PubMed articles published in the past 10 years, including clinical studies that assessed the effects of combination therapy with GLP-1 receptor agonists and SGLT-2 inhibitors in patients with type 2 diabetes.

Summary: Research indicates that the combination of GLP-1 receptor agonists and SGLT-2 inhibitors leads to improved glycaemic control, better lipid management, lower blood pressure, and reduced body weight. It also improves vascular and myocardial health markers, while reducing cardiovascular risk. Although this combination therapy benefits kidney health, certain areas remain unchanged. Considering all of this, combination therapy seems to be a promising treatment, offering greater benefits than other antidiabetic therapies.

Keywords: Drug Therapy, Combination; Glucagon-Like Peptide-1 Receptor Agonists; Sodium-Glucose Transporter 2 Inhibitors; Diabetes Mellitus, Type 2; Heart Disease Risk Factors.

Introduction

The worldwide increase in the prevalence of obesity and sedentary lifestyle has led to the ongoing increase in the incidence of type 2 diabetes.[1,2] It is estimated that 462 million individuals are affected by type 2 diabetes globally, which is equivalent to 6.28% of the world's population.[3] Furthermore, diabetes and its complications generate high costs not only for the patients themselves but also for their families, health systems, and national economies. This occurs through the direct costs of treating the disease itself as well as its complications, and also as a result of incapacity to work whether lost productivity due to premature mortality.[4,5] Type 2 diabetes affects almost every organ of the human body in the long term and increases the overall risk of dying prematurely. The most common chronic complications of type 2 diabetes are broadly divided into two main categories: macroangiopathy, which includes conditions such as stroke, coronary heart disease and hypertension, and microangiopathy, which comprises diabetic retinopathy, nephropathy and neuropathy. Vulnerability to infections, myopathy, osteoporosis, arthropathies and liver damage are also noted.[6] All this argues in favour of using the most effective treatment for type 2 diabetes.

Current guidelines do suggest the use of glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose cotransporter-2 (SGLT-2) inhibitors in combination among patients with type 2 diabetes with or at high risk for atherosclerotic cardiovascular disease (ASCVD), heart failure, or chronic kidney disease (CKD), as part of the comprehensive approach to cardiovascular and kidney risk reduction.[7–9] This approach is supported by the results from more than one meta-analysis. The 2019 meta-analysis showed that both classes of GLP-1 receptors agonist and SGLT-2 inhibitors reduced the risk of major adverse cardiovascular events (MACE) by approximately 14% in patients with known ASCVD.[10] Also, the 2021 meta-analysis showed with high certainty that adding a GLP-1 receptor agonist or SGLT-2 inhibitor to the treatment of type 2 diabetes reduces mortality, non-fatal myocardial infarction, renal failure and severe hyperglycaemia.[11]

This review aims to collect data on the effects of combined treatment with GLP-1 receptor agonists and SGLT-2 inhibitors among patients with type 2 diabetes mellitus with special emphasis on the impact on cardiovascular risk. We want to also highlight the importance of using the latest drugs with already proven beneficial effects on cardiovascular risk and renal function in this group of patients.

Materials and Methods

The review was conducted based on an analysis of materials obtained from PubMed. The following search terms were used: sodium-glucose cotransporter 2 inhibitors, SGLT-2 inhibitors, SGLT2 inhibitors, SGLT2i, glucagon-like peptide-1 receptor agonists, GLP-1 receptor agonists, GLP-1RAs, GLP1RAs. Only articles published within the last 10 years were included in the study. The search was limited to clinical studies examining the effects of combination therapy with GLP-1 agonists and SGLT-2 inhibitors in patients with type 2 diabetes mellitus. Since this study was not designed as a meta-analysis, no statistical methods were applied. Additionally, this search was further complemented by a search for relevant articles in order to describe pathophysiology of type 2 diabetes mellitus and the mechanisms of action of these drug classes.

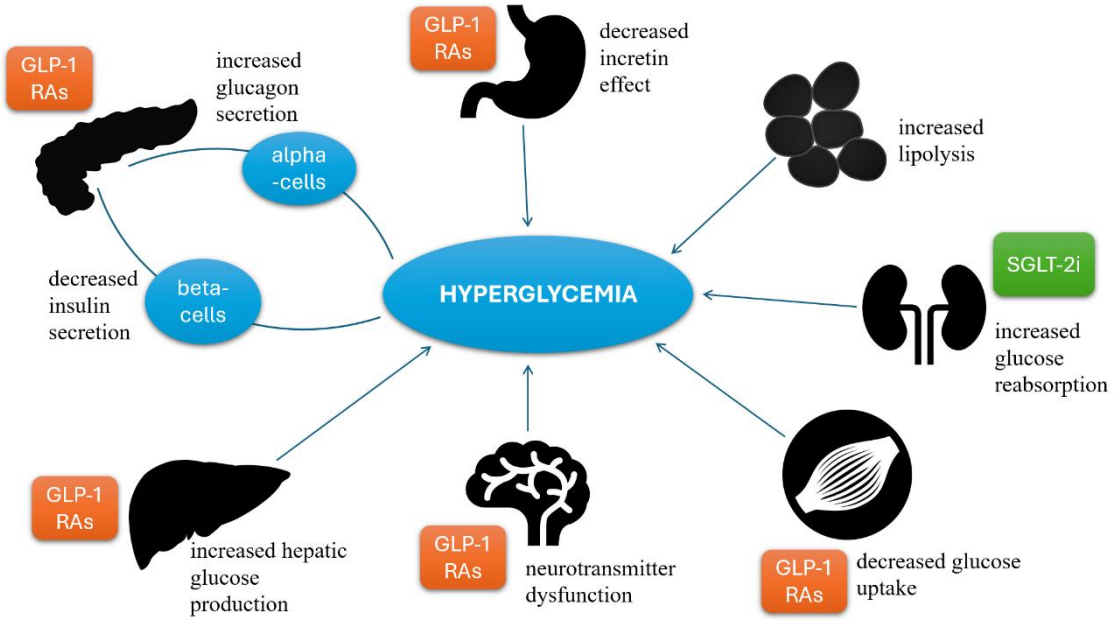
Pathophysiology of type 2 diabetes mellitus

Type 2 diabetes is associated with a number of factors that interfere with the body's ability to regulate blood sugar levels. These disturbances contribute to poor glucose control and can lead to both macrovascular and microvascular complications. The development of the disease is primarily due to two key issues: insulin resistance in peripheral tissues and beta-cell secretory failure.[12,13] Insulin resistance is defined as the impaired biological response of target tissues to insulin stimulation despite normal or elevated serum levels of this hormone.[14] Although any tissue with insulin receptors can become insulin resistance, the main tissues responsible for driving insulin resistance are the liver, skeletal muscles, and adipose tissue. In insulin resistance, the ability of target tissues to take up and use glucose decreases. As a result, lipolysis and the release of free fatty acids (FFAs) are increased in adipose tissue. At the same time, hepatic glycogenolysis, gluconeogenesis and the synthesis of very-low-density lipoprotein (VLDL) and triglycerides (TG) are increased.[12,15–18] Insulin resistance reduces the body's ability to process glucose effectively, leading beta-cells to produce more insulin as

compensation, which results in hyperinsulinemia.[19] Symptoms of diabetes develop when beta-cells do not secrete insulin in sufficient quantities to maintain glucose homeostasis, which means the loss of more than 80% of estimated beta-cell function.[20] In addition to the metabolic changes in muscle, liver, adipocytes and beta cells highlighted earlier, type two diabetes also results in deficiency or resistance to incretins in the gastrointestinal tract, increased glucagon secretion by pancreatic alpha-cells, increased renal glucose reabsorption, as well as insulin resistance and dysregulation of neurotransmitters in the central nervous system.[21]

Figure 1.

Mechanism and site of action of GLP-1 analogues and SGLT-2 inhibitors based on pathophysiological abnormalities present in type 2 diabetes.



Abbreviations: GLP-1 RAs, glucagon-like peptide-1 receptor agonists; SGLT-2i, sodium-glucose cotransporter-2 inhibitors.

Type 2 diabetes as an autoinflammatory disease caused by metabolic stress

As mentioned earlier, obesity is an established risk factor for type 2 diabetes.[22] However, it is primarily excess visceral adipose tissue, but not general adiposity, that is independently associated with type 2 diabetes in obese adults.[23] Nevertheless, obesity leads to adipose tissue dysregulation, resulting in decreased oxygen availability and hypoxia. This leads to the activation of hypoxia inducible factor 1α (HIF-1α), apoptosis-related genes, vascular

endothelial growth factor (VEGF), glucose transporters, and plasminogen activator inhibitor (PAI-1), and a decrease in adipocyte secretion of anti-inflammatory adipokines. Mitochondrial uncoupling, caused by excess nutrients and fatty acids (FA), leads to increased reactive oxygen species (ROS) production and abnormal signaling pathways involving nuclear factor-kappa B (NF-κB), causing vascular dysfunction, atherosclerosis, and inflammation. Activated adipocytes secrete pro-inflammatory cytokines like interleukin-1β (IL-1β) and tumour necrosis factor-α (TNFα), which signal through toll-like receptor 2/4 (TLR2/4) in muscle, liver, and adipose cells, promoting inflammation. This results in further infiltration of adipose tissue by macrophages which secrete TNF-α, IL-1, IL-6, and monocyte chemoattractant protein 1 (MCP-1) as well as immune cells (B cells and T cells) causing local and systemic chronic low-grade inflammation. It all leads to a link between obesity, insulin resistance and the onset of type two diabetes.[24,25]

Mechanism of action of GLP-1 receptor agonists

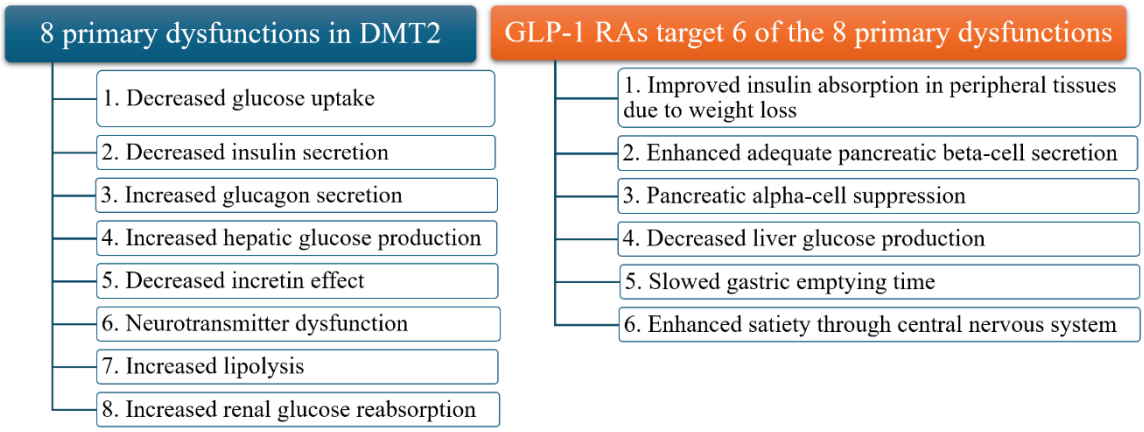
Glucagon-like peptide 1 (GLP-1) is synthesized by alpha cells of pancreas, the nucleus of the solitary tract (TNS) in the brainstem, as well as by enteroendocrine GLP-1 producing cells (GLP-1 EECs) within the small intestine and the colon. Secretion of GLP-1 is triggered by consumption of meal containing carbohydrates, proteins and fats. GLP-1 has particularly short half-life of between 2 and 11 minutes due to inactivation by dipeptidyl-peptidase 4 (DPP 4). Through structural modifications, therapeutic GLP-1 receptor agonists become resistant to inactivation by DPP-4 while still retaining affinity for the receptor for GLP-1.[26]

Receptors for GLP-1 are widely expressed in various tissues throughout the body, playing critical roles in numerous physiological processes. They are found, for instance, in pancreatic islet cells, as well as cells in the brain, lungs, heart, kidney, and gastrointestinal tract.[27]

GLP-1 receptor agonists increase insulin secretion in response to carbohydrates in a meal and prevent postprandial hyperglycaemia. In addition, they inhibit glucagon secretion by pancreatic beta cells and reduce hepatic glucose production. Since GLP-1 receptor agonists regulate insulin and glucagon secretion based on glucose levels, they are associated with a lower risk of hypoglycaemia compared to conventional antidiabetic agents like insulin or sulfonylureas. GLP-1 receptor agonists also enhance satiety through a hypothalamic mechanism by inhibiting the appetite centre, as well as delaying gastric emptying. This results in a weight loss and improvement in insulin sensitivity.[28–30]

Figure 2.

GLP-1 receptor agonists effect and sites of action in type 2 diabetes.



Abbreviations: GLP-1 RAs, glucagon-like peptide-1.

Mechanism of action of SGLT-2 inhibitors

Sodium-glucose cotransporter-2 (SGLT-2) is transmembrane protein almost exclusively expressed in the apical membrane of renal proximal convoluted tubule. SGLT2 uses a sodium gradient, created by the sodium-potassium ATPase pump, to transport glucose against its concentration gradient. For every molecule of glucose reabsorbed, SGLT2 co-transports one sodium ion.[31]

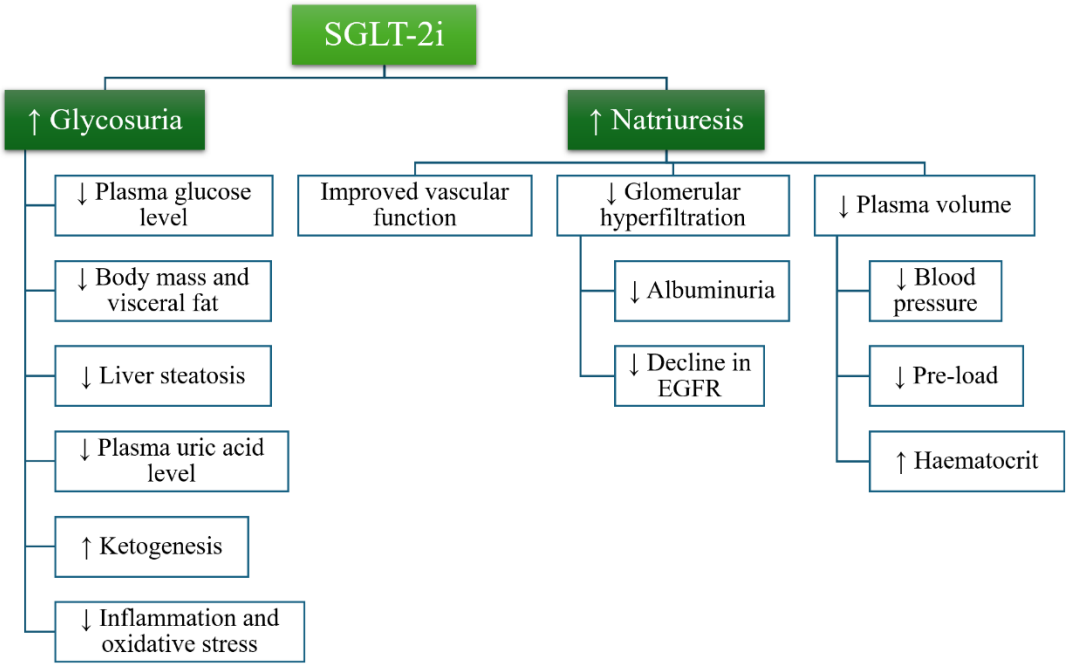
It is estimated that approximately 90% of tubular glucose reabsorption is via SGLT2.[32] The normal renal threshold for reabsorption of glucose corresponds to a serum glucose concentration of 180 mg/dL.[33] However, in individuals with type 2 diabetes, this threshold can become elevated, and the SGLT2 expression may increase. This maladaptive response leads to increased glucose reabsorption, further exacerbating hyperglycaemia.[34]

SGLT-2 inhibitors reduce renal tubular glucose reabsorption, increasing glycosuria, which results in a reduction of blood glucose levels without stimulating insulin release. Since their action is independent of β-cell function, this class of drugs is associated with a low risk of hypoglycaemia. They also decrease plasma uric acid level by reducing urate absorption in the proximal convoluted tubule. In addition, SGLT-2 inhibitors have demonstrated additional

metabolic benefits of weight loss due to caloric loss and blood pressure reduction through a modest diuretic effect. By inducing natriuresis, they not only reduce plasma volume, hence reduced cardiac preload, but also cause an increase in haematocrit, reduce glomerular hyperfiltration and decrease albuminuria. Furthermore, SGLT-2 inhibitors increase ketone bodies production which are metabolic substrates for the heart and kidney. Additionally, they reduce liver steatosis in type 2 diabetes patients with non-alcoholic fatty liver disease. Other suggested beneficial effects of SGLT2 inhibitors include decreased adipose tissue mediated inflammation and proinflammatory cytokine production, as well as reduced oxidative stress. Moreover, several studies have shown that SGLT-2 inhibitors improve endothelial function and reduce vascular stiffness by suppressing the reaction cascade of advanced glycation end products (AGEs) and their receptors (RAGEs), known as the AGE–RAGE signaling pathway.[35–37]

Figure 3.

Pleiotropic effects of SGLT2 inhibitors in multiple organ systems and metabolic pathways.



Abbreviations: SGLT-2i, sodium-glucose cotransporter-2 inhibitors.

Effects of combined treatment with GLP-1 receptor agonists and SGLT-2 inhibitors among patients with type 2 diabetes mellitus

Metabolic outcomes

A fundamental goal of type 2 diabetes management is achieving effective glycaemic control based on individualized glycated haemoglobin (HbA1c) targets to reduce the risk of complications and improve overall health outcomes.[38] Therefore, changes in HbA1c levels are often the primary endpoint in many studies.

The DURATION-8 study, a multicenter, double-blind, randomized, phase 3 trial, involved 695 adults with type 2 diabetes and inadequate glycaemic control despite stable metformin monotherapy. The participants were randomly assigned to one of three groups: exenatide 2 mg once weekly plus dapagliflozin 10 mg once-daily (n = 228), exenatide once weekly plus placebo (n = 227), or dapagliflozin plus placebo (n = 230). A total of 431 patients (62.0%) completed the 104-week treatment period. The reduction in HbA1c from baseline to 104 weeks was greater with the combination of exenatide once weekly plus dapagliflozin (-1.70% [0.11]) compared to exenatide once weekly plus placebo (-1.29% [0.12]; P = 0.007) and dapagliflozin plus placebo (-1.06% [0.12]; P < 0.001). Clinically meaningful improvements were also observed in fasting plasma glucose (FPG), 2-h postprandial glucose (2-h PPG), body weight, and systolic blood pressure (SBP) with the exenatide and dapagliflozin combination.[39] The AWARD-10 study, another double-blind, randomised, placebo-controlled trial, was a 24-week phase 3 trail involving 424 patients with type 2 diabetes inadequately controlled with SGLT-2 inhibitors, with or without metformin. Participants were randomly assigned to one of three groups: dulaglutide 1.5 mg once-weekly (n=142), dulaglutide 0.75 mg (n=142) once-weekly, or placebo (n=140), while continuing their ongoing treatment regimen. The reduction in HbA1c from baseline to 24 weeks was significantly larger in patients receiving either dose of dulaglutide compared to those receiving placebo (p<0.0001). Additionally, patients receiving dulaglutide 1.5 mg showed significantly greater decreases in body weight (p = 0.028), FPG (p < 0.0001), and SBP (p = 0.021) compared to those receiving placebo.[40]

In the SUSTAIN 9 study, a multicenter, double-blind, randomised, 30-week phase 3 trail, 302 patients with type 2 diabetes treated with SGLT-2 inhibitors were enrolled. The results showed that adding semaglutide to ongoing treatment was associated with significant reductions in HbA1c, body weight, low density lipoprotein (LDL) cholesterol concentrations, and SBP compared to placebo.[41]

Furthermore, a 52-week, open-label phase 4 study involving 71 Japanese patients with type 2 diabetes and inadequate glycaemic control on GLP-1 receptor agonist therapy found that the addition of canagliflozin resulted in significant reductions in HbA1c, FPG, body weight, SBP, as well as an increase in high-density lipoprotein (HDL) cholesterol level.[42]

Similarly, another 52-week, open-label clinical study involving 76 Japanese patients with type 2 diabetes inadequately controlled on liraglutide monotherapy, found that adding luseogliflozin led to greater reductions in HbA1c, FPG, and body weight.[43]

In a retrospective, observational, multicenter real-world study conducted by a network of Diabetes Centers in Lombardy, patients with obesity and type 2 diabetes mellitus who were treated with SGLT-2 inhibitors (with or without other anti-diabetic medications) had dulaglutide 1.5 mg once-weekly added to their treatment. A total of 334 patients were followed up after 6 months, showing significant reductions in HbA1c levels, body mass index and body weight.[44]

According to pre-post observational study involving 75 patients with type 2 diabetes and a minimum of one year of treatment with a GLP-1 receptor agonist, the addition of canagliflozin to ongoing therapy was associated with significant reductions in HbA1c, body weight, SBP, and diastolic blood pressure (DBP), as well as a significant increase in mean HDL cholesterol levels.[45]

A study conducted in Texas found that adding combination therapy with dapagliflozin and exenatide to basal therapy resulted in greater improvements in glycaemic control compared to adding either dapagliflozin or exenatide alone.[46]

Furthermore, other studies have demonstrated that combination therapy with GLP-1 receptor agonists and SGLT-2 inhibitors significantly improves glycaemic control and promotes weight reduction.[47–51]

Cardiovascular outcomes

Diabetes is a significant independent risk factor for atherosclerotic cardiovascular disease (ASCVD), which remains the leading cause of mortality in this population. Individuals with type 2 diabetes often present with major cardiovascular risk factors, including hypertension, hyperlipidaemia, and obesity. Consequently, comprehensive management of these risk factors, including glycaemic control, blood pressure regulation, and lipid management, is essential.[52]

According to the CANVAS Program, which included two double-blind, randomized, placebo-controlled trials (CANVAS and CANVAS-R) involving 407 patients with type 2 diabetes using GLP-1 receptor agonist at baseline and elevated cardiovascular risk, the addition of canagliflozin to ongoing GLP-1 receptor agonist therapy showed no clinically meaningful changes in UACR (P = 0.21), eGFR (P = 0.72), or major adverse cardiovascular events (P = 0.94). However, greater reductions were observed with canagliflozin compared to placebo in HbA1c (-0.75% vs. -0.58%; P = 0.0091), SBP (−6.26 vs. −3.83 mmHg; P = 0.0018), and body weight (-3.79 vs. -2.18 kg; P < 0.0001) among those on baseline GLP-1 receptor agonist therapy.[47]

In contrast to the Canvas program, a cohort study conducted in the United Kingdom demonstrated that the GLP-1 receptor agonist and SGLT-2 inhibitor combination was associated with a lower risk of major adverse cardiovascular events (MACE) and serious renal events compared with either drug class used alone. The study assembled two prevalent cohorts: the first included 6,696 patients who initiated GLP-1 receptor agonists and subsequently added SGLT-2 inhibitors, while the second comprised 8,942 patients who started SGLT-2 inhibitors and later added GLP-1 receptor agonists. The combination of SGLT-2 inhibitors and GLP-1 receptor agonists was associated with a 30% lower risk of MACE (7.0 vs. 10.3 events per 1,000 person-years; hazard ratio [HR] 0.70, 95% confidence interval [CI] 0.49-0.99) and a 57% lower risk of serious renal events (2.0 vs. 4.6 events per 1,000 person-years; HR 0.43, 95% CI 0.23-0.80) compared with GLP-1 receptor agonists alone. Similarly, compared with SGLT-2 inhibitor monotherapy, the GLP-1 receptor agonist and SGLT-2 inhibitor combination therapy was associated with a 29% lower risk of major adverse cardiovascular events (7.6 vs. 10.7 events per 1,000 person-years; HR 0.71, 95% CI 0.52-0.98), while the reduction in serious renal events had a wider confidence interval (1.4 vs. 2.0 events per 1,000 person-years; HR 0.67, 95% CI 0.32-1.41).[53]

Another study supporting the beneficial effects of combined treatment with GLP-1 receptor agonists and SGLT-2 inhibitors on reducing the risk of MACE is a multicentre, prospective observational study published in 2024. The study involved 512 patients with type 2 diabetes, already receiving either an SGLT-2 inhibitor or a GLP-1 receptor agonist, who had experienced acute myocardial infarction (AMI) and undergone percutaneous coronary intervention. The findings demonstrated that the incidence of MACE was significantly lower in the combination therapy group compared to patients treated with a GLP-1 receptor agonist alone (HR 0.154, 95% CI 0.038-0.622; P = 0.009) and those treated with an SGLT-2 inhibitor alone (HR 0.170, 95% CI 0.046-0.633; P = 0.008). Additionally, the myocardial salvage index

(MSI) and the proportion of patients with MSI > 50% was higher in the combination therapy group compared to those treated with either drug class alone.[54]

In a randomized trial involving 200 individuals with type 2 diabetes, poor glycaemic control on metformin, and high or exceptionally high cardiovascular risk, six months of treatment with a combination of liraglutide and empagliflozin resulted in greater improvements in left atrial function compared to either drug alone or insulin, despite similar HbA1c reductions across all groups. Additionally, the combination therapy group demonstrated improvements in arterial stiffness, evidenced by a reduction in pulse wave velocity (PWV), and a decrease in central SBP.[48]

Another randomized trial involving 180 subjects with type 2 diabetes, poor glycaemic control and high or very high cardiovascular risk, confirmed that patients treated with a combination of GLP-1 receptor agonists and SGLT-2 inhibitors for 12 months achieved greater reductions in PWV, and central SBP, as well as greater improvements in endothelial glycocalyx thickness, compared with patients treated with insulin. Moreover, patients receiving combination therapy showed a greater increase in myocardial work index than those treated with insulin or SGLT-2 inhibitor alone, despite similar reductions in HbA1c levels. Additionally, patients on combination therapy demonstrated greater reductions in PWV and SBP compared to those treated with insulin or GLP-1 receptor agonist, respectively.[49]

In contrast, a randomised, 32-week trial conducted in Denmark involving 120 people with type 2 diabetes at high cardiovascular risk found no evidence that combination treatment with empagliflozin and semaglutide reduces arterial stiffness. However, the combined treatment resulted in a significant and clinically meaningful reduction in SBP compared to placebo, empagliflozin alone, or semaglutide alone.[50]

Other studies, including those referenced in the "Metabolic Outcomes" paragraph, have demonstrated that combination therapy with GLP-1 receptor agonists and SGLT-2 inhibitors reduces SBP.[39–42,45,51,55]

Renal outcomes

One of the complications of type 2 diabetes is diabetic nephropathy, which can lead to renal insufficiency.[6] Effective management of diabetes is essential to prevent or slow the progression of nephropathy, as uncontrolled blood sugar levels and associated factors like hypertension accelerate kidney damage.[56]

In a prespecified secondary analysis of the 16-week randomized DECREASE trial, which enrolled 66 obese patients with poorly controlled type 2 diabetes, the combination of exenatide and dapagliflozin led to greater reductions in albuminuria, estimated glomerular filtration rate (GFR), kidney injury molecule-1(KIM-1) compared to either drug alone or placebo.[51]

According to the previously mentioned 32-week randomized trial conducted in Denmark, the urinary albumin-to-creatinine ratio (UACR) decreased by 36% (95% CI 4-57; $p = 0.03$) in the empagliflozin and semaglutide combination group compared with placebo.[50] Additionally, a post hoc analysis of this trial revealed that combined therapy reduced cortical apparent diffusion coefficient (ADC), indicating kidney microstructural changes unrelated to GFR, albuminuria, or inflammation. Furthermore, total kidney volume (TKV) decreased across all active treatment groups, possibly due to reduced hyperfiltration.[57] However, data from the same trial indicated that combination of empagliflozin and semaglutide, did not improve medullary kidney oxygenation compared to placebo in a individuals with type 2 diabetes and normal to slightly reduced kidney function.[58]

Summary

Most studies show that combining GLP-1 receptor agonists and SGLT-2 inhibitors provides additive benefits for glycaemic control, lipid management, blood pressure, and body weight reduction. This combination therapy also leads to greater improvements in vascular and myocardial health markers and reduces cardiovascular risk compared to either drug alone. Additionally, while the combination improves certain aspects of kidney health in patients with type 2 diabetes, some areas remain unaffected. Overall, the combined therapy may help protect kidney function in this population.

In summary, the synergistic effects of GLP-1 receptor agonists and SGLT-2 inhibitors on the progression of type 2 diabetes make this combination an effective treatment strategy for achieving lasting glycaemic control, reducing diabetes-related complications, and lowering cardiovascular risk. However, additional long-term clinical studies are needed to further evaluate the effects of GLP-1 receptor agonists and SGLT-2 inhibitors combination therapy, particularly regarding cardiovascular risk and renal effects in patients with type 2 diabetes.

Disclosure:

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