BG Pulse Journal USA
ISSN:1947-2536 http://www.bgpulseusa.com/index.php/bg
BG PULSE JOURNAL

COMPARATIVE EVALUATION OF THE SINGLE AND COMBINED EFFECTS OF GLP-1 RECEPTOR AGONISTS AND SGLT2 INHIBITORS

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Abstract: Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder characterized by insulin resistance, impaired β-cell function, excess body weight, and the development of cardiovascular and renal complications. In recent years, pharmacotherapeutic approaches aimed not only at improving glycemic control but also at reducing cardiorenal and metabolic risks have been increasingly developed. GLP-1 receptor agonists and sodium-glucose cotransporter 2 (SGLT2) inhibitors play an important role in this therapeutic approach. This article provides a comparative analysis of the effects of GLP-1 receptor agonists and SGLT2 inhibitors used as monotherapies and in combination on glycemic control, body weight, arterial blood pressure, lipid metabolism, and renal function. GLP-1 receptor agonists primarily improve glycemic control by enhancing glucose-dependent insulin secretion, suppressing glucagon secretion, and slowing gastric emptying, while also contributing to body weight reduction. SGLT2 inhibitors, in contrast, reduce renal glucose reabsorption and exert their effects through insulin-independent glycosuria, while providing important cardiorenal protective benefits. Because these two pharmacological classes have distinct and complementary mechanisms of action, their combination represents a promising therapeutic approach for achieving comprehensive metabolic control.

Keywords: type 2 diabetes mellitus, GLP-1 receptor agonists, SGLT2 inhibitors, semaglutide, liraglutide, dapagliflozin, empagliflozin, combination therapy, glycemic control, body weight, cardiorenal protection.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the most common metabolic disorders worldwide. Insulin resistance, impaired secretory function of pancreatic β-cells, and disturbances in glucose metabolism play a key role in its development. Long-term persistence of the disease increases the risk of complications such as cardiovascular disease, heart failure, and chronic kidney disease [1,2]. Although metformin, sulfonylureas, and other antidiabetic agents have traditionally been widely used to achieve glycemic control, modern diabetology increasingly emphasizes treatment selection based not only on the ability to reduce HbA1c levels but also on the effects of pharmacological agents on body weight, cardiovascular risk, and renal function [3]. GLP-1 receptor agonists mimic the physiological mechanisms of the incretin system. They enhance glucose-dependent insulin secretion, suppress glucagon secretion, slow gastric emptying, and reduce appetite through central

mechanisms. As a result, they improve glycemic control and may contribute to body weight reduction [4,5]. SGLT2 inhibitors, in contrast, reduce glucose reabsorption in the proximal renal tubules. This results in increased urinary glucose excretion, reduced glycemic load, and additional natriuresis and osmotic diuresis [6–8]. These mechanisms contribute to the beneficial effects of these agents on blood pressure and clinical outcomes associated with heart failure [9,10]. Therefore, the combined use of a GLP-1 receptor agonist and an SGLT2 inhibitor theoretically integrates two distinct but complementary pharmacological mechanisms. The aim of this article is to comparatively evaluate the effects of these agents as monotherapy and combination therapy on key metabolic and cardiorenal parameters.

AIM OF THE STUDY

The aim of the study was to comparatively evaluate changes in glycemic, metabolic, hemodynamic, and renal parameters during monotherapy and combination therapy with a GLP-1 receptor agonist and an SGLT2 inhibitor, and to determine the potential advantages of combination therapy.

MATERIALS AND METHODS

In this study, the pharmacological properties of GLP-1 receptor agonists and SGLT2 inhibitors, as well as their effects under conditions of monotherapy and combination therapy, were analyzed based on contemporary clinical studies and scientific literature.

The following main parameters were selected for comparative evaluation:

glycated hemoglobin (HbA1c);
fasting blood glucose;
body weight and body mass index;
systolic and diastolic blood pressure;
lipid profile;
serum creatinine;
estimated glomerular filtration rate (eGFR);
cardiovascular risk;
risk of hypoglycemia;
adverse effects.

From a pharmacological perspective, the following treatment groups were compared: Group I: GLP-1 receptor agonist;

Group II: SGLT2 inhibitor;

Group III: GLP-1 receptor agonist + SGLT2 inhibitor combination;

Group IV: standard glycemic therapy.

Semaglutide or liraglutide were considered as representative GLP-1 receptor agonists, while empagliflozin or dapagliflozin were considered as representative SGLT2 inhibitors.

PHARMACOLOGICAL EFFECTS OF GLP-1 RECEPTOR AGONISTS

GLP-1 receptor agonists enhance the biological effects of endogenous GLP-1. Their principal mechanism of action is the stimulation of insulin secretion in a glucose-dependent manner.

The major pharmacological effects include:

1. enhancement of glucose-dependent insulin secretion;
2. suppression of glucagon secretion;
3. delayed gastric emptying;
4. reduction of appetite;
5. promotion of body weight loss;
6. reduction of HbA1c levels.

One of the important advantages of GLP-1 receptor agonists is their ability to reduce body weight. This characteristic is of particular clinical importance in patients with T2DM accompanied by overweight or obesity.

PHARMACOLOGICAL EFFECTS OF SGLT2 INHIBITORS

SGLT2 inhibitors exert their primary pharmacological effect in the proximal renal tubules by selectively inhibiting sodium-glucose cotransporter 2 (SGLT2), which is responsible for the majority of glucose reabsorption in the kidneys. Inhibition of this transporter reduces renal glucose reabsorption and increases urinary glucose excretion, thereby lowering plasma glucose levels through an insulin-independent mechanism.\

The principal pharmacological effects of SGLT2 inhibitors include:

1. reduction of renal glucose reabsorption;
2. enhancement of urinary glucose excretion;
3. reduction of plasma glucose and HbA1c levels;
4. mild reduction in body weight;
5. reduction of systolic and diastolic blood pressure;
6. induction of natriuresis and osmotic diuresis;
7. reduction of intraglomerular pressure;
8. preservation of renal function and slowing of chronic kidney disease progression;
9. reduction of the risk of hospitalization due to heart failure;
10. reduction of cardiovascular and renal complications in appropriate patient populations.

An important characteristic of SGLT2 inhibitors is that their glucose-lowering effect does not depend directly on pancreatic β-cell insulin secretion. Therefore, they can retain their pharmacological efficacy in patients with progressive β-cell dysfunction. In addition, the natriuretic and osmotic diuretic effects of these drugs contribute to reduced plasma volume and cardiac preload, which partly explains their beneficial effects in patients at risk of or with heart failure.

Unlike GLP-1 receptor agonists, the primary mechanism of SGLT2 inhibitors is not mediated through the gastrointestinal tract or central appetite-regulating pathways. Consequently, their effects on body weight are generally moderate, whereas their cardiorenal benefits may extend beyond their glucose-lowering activity.

PHARMACOLOGICAL EFFECTS OF SGLT2 INHIBITORS

SGLT2 is responsible for the reabsorption of a large proportion of filtered glucose in the proximal renal tubules. SGLT2 inhibitors block this transport mechanism, thereby increasing urinary glucose excretion.

Their main pharmacological effects include:

glycosuria;
reduction of blood glucose levels;
reduction in body weight;
natriuresis;
osmotic diuresis;
reduction in arterial blood pressure;
reduction in the risk of heart failure-related events;
contribution to long-term preservation of renal function.

An important characteristic of SGLT2 inhibitors is that their glucose-lowering effect is not directly dependent on insulin secretion.

COMPARATIVE EFFECTS OF GLP-1 RECEPTOR AGONISTS AND SGLT2 INHIBITORS

Parameter GLP-1 receptor agonist SGLT2 inhibitor Combination

HbA1c Marked reduction Moderate reduction Additional improvement in glycemic control

Fasting blood glucose Reduced Reduced Greater glycemic control

Body weight May decrease substantially Moderate reduction Potential additional weight reduction

Blood pressure Moderate effect May reduce blood pressure Comprehensive effect

Lipid profile Positive metabolic effects Favorable changes in some parameters Comprehensive metabolic effect

Renal protection Indirect and agent-dependent Strong cardiorenal effects Potential additive protection

Heart failure Cardiovascular benefit is agent-dependent Significant clinical benefit Comprehensive cardiorenal effect

Hypoglycemia Low risk with monotherapy Low risk with monotherapy Low risk in the absence of insulin/sulfonylureas

Main adverse effects Nausea, vomiting, gastrointestinal symptoms Genital infections, polyuria, dehydration Risks characteristic of both classes

PHARMACOLOGICAL BASIS OF COMBINATION THERAPY

The combination of a GLP-1 receptor agonist and an SGLT2 inhibitor integrates two distinct pharmacological mechanisms.

GLP-1 receptor agonists primarily regulate glycemia through the gut–pancreas–brain axis, whereas SGLT2 inhibitors act through the renal mechanism of increasing urinary glucose excretion.

Thus, combination therapy may produce a comprehensive pharmacological effect:

GLP-1 receptor agonist → insulin ↑, glucagon ↓, appetite ↓+

SGLT2 inhibitor → glycosuria ↑, natriuresis ↑↓

Improved glycemic control + body weight reduction + cardiorenal benefits

Another potential advantage of combination therapy is that certain metabolic changes associated with SGLT2 inhibitors may be partially counterbalanced by the effects of GLP-1 receptor agonists. However, it cannot be concluded that combination therapy will provide the same degree of efficacy in all patients. The choice of therapy should be based on the individual clinical characteristics and therapeutic needs of each patient.

GLYCEMIC CONTROL

GLP-1 receptor agonists and SGLT2 inhibitors differ in their mechanisms of reducing HbA1c levels. GLP-1 receptor agonists influence insulin secretion and glucagon regulation, whereas SGLT2 inhibitors enhance renal glucose excretion.

Therefore, their combined use may improve glycemic control through the complementary effects of these different mechanisms.

In particular, this combination may represent a pharmacologically rational therapeutic approach in patients with inadequate HbA1c control despite background therapy, especially those who are overweight or obese.

BODY WEIGHT AND METABOLIC EFFECTS

The weight-reducing effect of GLP-1 receptor agonists is primarily associated with appetite suppression and reduced food intake.

In SGLT2 inhibitors, body weight reduction is mainly related to urinary glucose loss and osmotic diuresis.

Therefore, combination therapy integrates two different mechanisms contributing to body weight reduction. However, changes in body weight also depend on factors such as the specific drug used, baseline body weight, dietary intake, and physical activity.

CARDIORENAL EFFECTS

One of the most important clinical characteristics of SGLT2 inhibitors is their association with cardiorenal protection. Their effects on natriuresis and osmotic diuresis help reduce cardiac preload and afterload. In addition, these agents can lower intraglomerular pressure and contribute to the preservation of renal function.

GLP-1 receptor agonists, particularly those with demonstrated cardiovascular benefit, may additionally contribute to the reduction of cardiovascular risk through improvements in body weight, glycemic control, and other metabolic parameters.

Consequently, the combination of GLP-1 receptor agonists and SGLT2 inhibitors may provide a complementary approach in patients with T2DM who require simultaneous management of hyperglycemia, excess body weight, cardiovascular risk, and renal complications.

CARDIORENAL EFFECTS

GLP-1 receptor agonists have also demonstrated cardiovascular benefits in certain agents, including reductions in cardiovascular risk and major adverse cardiovascular outcomes in appropriate patient populations.

Therefore, the combination of these two drug classes is of particular interest not only for glycemic control but also for the comprehensive management of cardiovascular and renal risks.

DISCUSSION

GLP-1 receptor agonists and SGLT2 inhibitors have distinct but complementary mechanisms of action in the modern pharmacotherapy of type 2 diabetes mellitus.

The major advantages of GLP-1 receptor agonists are associated with improved glycemic control and substantial body weight reduction, whereas the principal benefits of SGLT2 inhibitors are predominantly related to their cardiorenal effects.

From this perspective, the combined use of these agents should not be regarded solely as a strategy for reducing HbA1c, but rather as a comprehensive therapeutic approach aimed at simultaneously managing metabolic, cardiovascular, and renal risks.

However, when evaluating the efficacy and appropriateness of combination therapy, several patient-specific factors should be taken into consideration, including age, renal function, the presence of cardiovascular disease, body weight, dietary habits, and concomitant medications.

The complementary mechanisms of action of these two pharmacological classes provide a rational basis for their combined use. GLP-1 receptor agonists predominantly influence glucose-dependent insulin secretion, glucagon suppression, appetite regulation, and body weight, whereas SGLT2 inhibitors promote urinary glucose and sodium excretion and exert important hemodynamic and renal effects. Consequently, their combination may provide broader metabolic and cardiorenal benefits than either class alone in appropriately selected patients.

At the same time, combination therapy should not be considered universally superior for every patient. The expected clinical benefit depends on the specific GLP-1 receptor agonist and SGLT2 inhibitor used, baseline cardiovascular and renal status, glycemic targets, body weight, tolerability, and concomitant antidiabetic treatment. Further evidence from long-term comparative and randomized clinical studies is therefore important for defining the optimal patient populations and treatment strategies.

CONCLUSION

GLP-1 receptor agonists and SGLT2 inhibitors possess distinct but complementary pharmacological mechanisms in the treatment of type 2 diabetes mellitus.

GLP-1 receptor agonists offer important advantages in improving glycemic control and reducing body weight, whereas SGLT2 inhibitors are characterized by glucose-lowering effects combined with clinically important cardiorenal protective properties.

The combination of these two pharmacological classes represents a promising therapeutic strategy for improving glycemic control, promoting body weight reduction, and comprehensively managing cardiovascular and renal risks.

Nevertheless, further large-scale, long-term randomized clinical trials are required to determine the clinical efficacy and safety of specific GLP-1 receptor agonist–SGLT2 inhibitor combinations and to identify the patient populations most likely to derive the greatest benefit from this therapeutic approach.

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