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The Application of Incretin-Based Pharmacotherapy in the Contemporary Management of Type 2 Diabetes: A Review of the Literature

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Abstract

Introduction

Type 2 diabetes is a critical global health issue due to its rising prevalence and severe complications, including cardiovascular diseases, chronic kidney disease, and neuropathies, which reduce quality of life and increase mortality risk. While metformin remains a cornerstone of treatment, incretin-based therapies like GLP-1 receptor agonists and DPP-4 inhibitors provide additional benefits, including glycemic control, weight management, and organ protection, making them essential in personalized care.

Aim of the Study

This study evaluates the mechanisms, efficacy, and benefits of GLP-1 receptor agonists and DPP-4 inhibitors in improving glycemic control, reducing cardiovascular risk, managing weight, and protecting renal function.

Materials and Methods

Data was sourced from recent clinical trials and literature (post-2020) from PubMed, Google Scholar, Lancet, New England Journal of Medicine, Nature, American Diabetes Association, Research Gate.

Results

GLP-1 receptor agonists demonstrated significant benefits, including a 27% reduction in major adverse cardiovascular events (MACE), a 32% decrease in kidney disease progression, and notable weight loss (e.g., 15.2% with semaglutide). These drugs also improved glycemic and metabolic parameters, though initial gastrointestinal side effects were common but temporary. DPP-4 inhibitors showed nephroprotective effects, reducing albuminuria and slowing eGFR decline, and were associated with a lower hypoglycemia risk compared to sulfonylureas, particularly in advanced CKD. While less effective in weight management, they offered a weight-neutral option for patients with mild hyperglycemia or advanced CKD. GLP-1 receptor agonists are ideal for high-risk or obese patients due to their strong glycemic and weight benefits, whereas DPP-4 inhibitors are safer for those with advanced CKD.

Keywords:

Type 2 Diabetes, GLP-1 Receptor Agonists, DPP-4 Inhibitors, Incretin-Based Therapies, Glycemic Control, Cardiovascular Risk, Chronic Kidney Disease, Weight Management, Pharmacotherapy, Personalized Medicine

Introduction

In modern times, type 2 diabetes represents one of the greatest challenges facing contemporary healthcare systems. The significant rise in prevalence, affecting both developed and, increasingly, developing countries, necessitates innovative solutions in pharmacotherapy. Type 2 diabetes is a multifactorial disease associated not only with carbohydrate metabolism disorders but also with numerous complications such as cardiovascular diseases, chronic kidney disease, and neuropathies. [23] These complications are major contributors to the deterioration of patients' quality of life and increased mortality rates.

Traditional treatment methods, such as the use of metformin, which for many years formed the cornerstone of diabetes therapy, continue to play a pivotal role. However, they are

increasingly complemented by modern medications, such as incretin-based GLP-1 receptor agonists and DPP-4 inhibitors. These drugs offer new possibilities in the management of type 2 diabetes, enabling improved glycemic control while also providing additional benefits, including weight reduction (particularly with GLP-1 receptor agonists), reduction in cardiovascular risk (with selected agents), and nephroprotective effects. [27]. A modern approach to diabetes treatment emphasizes the individualization of therapy, enhancing its effectiveness and improving patients' quality of life.

Transformative Progress in Diabetes Treatment: From Metformin to Modern Therapies

In recent decades, the management of diabetes has improved significantly. Remarkable progress has been made since 1994, when the development of new antidiabetic drugs accelerated considerably. As a result, the number of registered antidiabetic medications has increased substantially, enabling the introduction of modern therapies tailored to patients' needs. [35]

Traditionally used sulfonylureas are gradually losing their significance in favor of newer medications, such as SGLT2 inhibitors and GLP-1 receptor agonists. Unlike sulfonylureas, these newer drugs are associated with a lower risk of hypoglycemia. However, metformin, which was introduced in 1957, remains a cornerstone of type 2 diabetes therapy and continues to be recommended by leading diabetes associations as a first-line treatment option. [24]

According to current guidelines from diabetes associations, the selection of pharmacological therapy for type 2 diabetes should be individualized based on the patient's clinical profile. Metformin is often the initial drug of choice; however, in patients with a high cardiovascular risk, SGLT2 inhibitors or GLP-1 receptor agonists are recommended due to their well-documented cardiovascular benefits. These drugs are particularly valuable in managing patients with cardiovascular comorbidities. [15]

Recent studies have confirmed that SGLT2 inhibitors and GLP-1 receptor agonists offer numerous health benefits, especially for individuals with multiple risk factors. Their introduction into diabetes treatment has significantly enhanced therapeutic options, providing modern and effective solutions for patients. [11]

Mechanism of Action and Effects of Key Incretin-Based Drugs

Incretin-based drugs regulate blood glucose levels through two primary mechanisms: GLP-1 receptor agonists mimic the action of endogenous GLP-1 by directly binding to its receptor, while DPP-4 inhibitors prevent the enzymatic degradation of endogenous GLP-1, thereby increasing its circulating levels. Both drug classes enhance glucose-dependent insulin secretion, offering an effective and safe approach to blood glucose regulation. [3,16]

GLP-1 Receptor Agonists: GLP-1 receptor agonists, such as Exenatide and Liraglutide, function by binding to specific GLP-1 receptors. This activation triggers a cascade of metabolic changes, including increased intracellular cyclic adenosine monophosphate (cAMP) levels, which stimulate glucose-dependent insulin secretion. Additional effects include suppression of glucagon secretion by pancreatic alpha cells, delayed gastric emptying, reduced appetite, and improved insulin sensitivity. While preclinical studies suggest that GLP-1 receptor agonists may promote beta-cell survival and proliferation, this has not been conclusively demonstrated in human trials.

DPP-4 Inhibitors: DPP-4 inhibitors, commonly referred to as "gliptins," such as Sitagliptin, Saxagliptin, and Vildagliptin, work by inhibiting the enzyme dipeptidyl peptidase-4, which degrades endogenous GLP-1. By preventing this degradation, DPP-4 inhibitors elevate circulating levels of incretin hormones, leading to glucose-dependent insulin secretion. [25] This glucose-dependent action is a key advantage, as it minimizes the risk of hypoglycemia compared to non-incretin-based therapies.

Incretin-based drugs provide a multifaceted approach to managing type 2 diabetes by improving glycemic control, suppressing glucagon secretion, and addressing challenges such as postprandial glucose spikes and weight management. Their mechanisms offer both efficacy and safety, making them valuable tools in diabetes care. [28]

The Cardiovascular Prognosis in Patients with Type 2 Diabetes and the Role of GLP-1 Analogues

In patients with type 2 diabetes, atherosclerosis is the most common cause of cardiovascular diseases. Studies suggest that up to 25% of asymptomatic patients with type 2 diabetes may

exhibit atherosclerotic changes in the coronary arteries, depending on diagnostic criteria and population characteristics. Cardiovascular complications are the leading cause of mortality in this patient group. The risk of hospitalization due to heart failure is approximately twofold higher in individuals with type 2 diabetes compared to non-diabetic individuals, while the risk of peripheral artery disease is estimated to increase by 2 to 4 times. Furthermore, the risk of stroke doubles within five years of a type 2 diabetes diagnosis compared to the general population. Given these associations, patients with type 2 diabetes are classified as having moderate or high cardiovascular risk, depending on additional comorbidities. [22]

In line with current cardiology and diabetology guidelines, patients with type 2 diabetes and coexisting atherosclerosis or high cardiovascular risk should be initiated on first-line therapy with GLP-1 analogues. This recommendation is supported by evidence showing that GLP-1 analogues reduce cardiovascular events and stabilize atherosclerotic plaques. The mechanisms of action include inhibiting atherosclerotic lesion formation, reducing pro-inflammatory markers through anti-proliferative effects on smooth muscle cells and vascular endothelium, mitigating oxidative stress, and increasing nitric oxide production. [10]

One of the latest clinical trials investigating GLP-1 analogues demonstrated that Efpeglenatide not only improves glycemic control but also offers multiple cardiovascular and renal benefits in patients at high risk for these complications. This study, published in 2021, included a large population of 4,076 patients with type 2 diabetes, including individuals with existing cardiovascular disease and/or chronic kidney disease. [17]

The trial evaluated the weekly administration of Efpeglenatide compared to placebo over a follow-up period of one year and eight months. The study demonstrated a 27% reduction in the risk of major adverse cardiovascular events (MACE), such as cardiovascular death, non-fatal myocardial infarction, and stroke, in the Efpeglenatide group. Additionally, renal benefits were observed, with a 32% reduction in the risk of kidney disease progression compared to the control group. Efpeglenatide demonstrated good tolerability, with gastrointestinal adverse events such as nausea and vomiting being the most commonly reported side effects, primarily during the initial phase of therapy. [32]

The Role of GLP-1 Analogues in Weight Reduction and Metabolic Improvement in Patients with Type 2 Diabetes

Overweight and obesity are significant challenges for patients with type 2 diabetes. Reducing excess body weight is a critical aspect of diabetes management, as it enhances the efficacy of pharmacotherapy and reduces the risk of complications. For many years, sulfonylurea derivatives, widely used in diabetes treatment, were associated with modest weight gain, which posed an additional challenge for weight management. An alternative to traditional treatments has emerged in the form of incretin-based therapies. Recent clinical studies have demonstrated the favorable impact of GLP-1 analogues on weight reduction. [7]

In clinical trials investigating semaglutide, particularly the STEP 5 program, significant weight reduction was observed among participants. This study, published in 2022, included 304 individuals without diabetes. The trial involved administering semaglutide via subcutaneous injections once weekly over two years, while the control group received a placebo. [1,6]

Participants in the STEP 5 program achieved a maximum weight loss of 15.3 kg, with an average percentage weight loss of 15.2%. In contrast, the control group receiving placebo experienced an average weight loss of 2.6%. The findings showed that 77.1% of participants achieved weight loss exceeding 5%, and 55.8% achieved weight reduction greater than 15%. [34]

Additionally, significant improvements in metabolic parameters were observed, including reductions in waist circumference and blood pressure. While glycemic control was not a focus of this trial, other studies involving diabetic patients have demonstrated improved HbA1c levels with GLP-1 analogue use. [26]

The GLP-1 analogue used in the trial was generally well-tolerated, with side effects primarily limited to mild to moderate gastrointestinal symptoms such as nausea and vomiting. These symptoms were most common during the initial dose-escalation phase and typically resolved with continued treatment. [29]

The Role of DPP-4 Inhibitors in Managing Diabetes in Patients with Chronic Kidney Disease

Dipeptidyl peptidase-4 (DPP-4) inhibitors play a critical role in managing type 2 diabetes mellitus (T2DM), particularly among patients with chronic kidney disease (CKD). These agents are favored due to their ability to provide effective glycemic control while maintaining a favorable safety profile, even in cases of moderate to severe renal impairment.

A meta-analysis conducted in 2021 assessed the renal and glycemic effects of DPP-4 inhibitors among patients with diabetes and CKD. The findings suggested that DPP-4 inhibitors reduce albuminuria and slow the progression of nephropathy in this population. Notably, they were associated with a modest but significant preservation of the estimated glomerular filtration rate (eGFR) compared to placebo or other glucose-lowering agents. [21]

Another recent study, published in 2022, investigated the safety outcomes of DPP-4 inhibitors in patients with advanced CKD. It found that the risk of hypoglycemia was substantially lower compared to sulfonylureas, which highlights the potential of DPP-4 inhibitors as a safer alternative for glycemic management in patients with compromised renal function. [33]

Moreover, a 2023 randomized controlled trial evaluated the long-term outcomes of patients on DPP-4 inhibitors and demonstrated improvements in microvascular complications, such as reductions in albuminuria, without adverse effects on cardiovascular health. [14] This positions DPP-4 inhibitors as a viable option not only for glucose control but also for renal and overall vascular protection in CKD patients.

The Comparative Characteristics of GLP-1 Analogues and DPP-4 Inhibitors in Type 2 Diabetes Management

Incretin-based drugs, GLP-1 analogues and DPP-4 inhibitors, share several similarities due to their interaction with glucagon-like peptide-1 (GLP-1). However, they differ significantly in their clinical effects and applications, particularly in areas such as appetite control, cardiovascular benefits, and glycemic control. [20]

GLP-1 analogues, unlike DPP-4 inhibitors, reduce appetite and significantly contribute to long-term weight reduction, making them particularly beneficial for patients with obesity. DPP-4 inhibitors, on the other hand, are weight-neutral, which can be advantageous for

patients not requiring weight loss. Additionally, GLP-1 analogues have demonstrated substantial benefits in reducing the risk of cardiovascular events, particularly in patients at high cardiovascular risk (e.g., semaglutide and liraglutide). While DPP-4 inhibitors do not provide consistent cardiovascular risk reduction, they are generally considered cardiovascularly neutral. However, some agents, such as saxagliptin, have been associated with an increased risk of heart failure, which should be taken into account when prescribing. [9]

One practical limitation of GLP-1 analogues is their subcutaneous route of administration, which may reduce adherence for some patients. However, the introduction of oral semaglutide has addressed this challenge for certain individuals. In contrast, DPP-4 inhibitors are administered orally, typically as a single daily tablet, significantly improving convenience and patient compliance. [5,12]

Current studies and the latest recommendations from diabetology societies indicate that GLP-1 analogues offer a stronger hypoglycemic effect compared to DPP-4 inhibitors. They achieve greater reductions in glycated hemoglobin (HbA1c), making them more effective for patients requiring stricter glycemic control. GLP-1 analogues also stand out due to their demonstrated nephroprotective effects, including the ability to reduce albuminuria and slow the progression of chronic kidney disease. Although DPP-4 inhibitors may offer some renal benefits, their nephroprotective effects are generally less pronounced and require further robust evidence. [4,8,13]

From a side-effect perspective, GLP-1 analogues are often associated with gastrointestinal disturbances, such as nausea and vomiting, particularly during the initial phase of treatment or dose escalation. These side effects can lead some patients to consider discontinuing therapy. Conversely, DPP-4 inhibitors are well-tolerated and are not associated with significant adverse effects, making them a safer choice for patients at risk of side effects or with lower tolerance for aggressive treatment. [19]

Patient Selection and Clinical Applications

- **DPP-4 inhibitors** are preferable for patients with mild hyperglycemia, older adults, individuals with pre-existing renal insufficiency, or those who may not tolerate

gastrointestinal side effects. They are particularly suited for patients not requiring weight loss or significant glycemic reductions. [53]

- **GLP-1 analogues**, on the other hand, are indicated for more advanced cases requiring stronger hypoglycemic effects. They are especially beneficial for obese patients, those with high cardiovascular risk, and individuals with early stages of chronic kidney disease where nephroprotective effects are critical. [30]

While both drug classes play a valuable role in type 2 diabetes management, their distinct profiles make them suitable for different patient populations. Understanding these differences allows for better tailoring of therapy, improving patient outcomes and adherence. [31]

Conclusion

Type 2 diabetes remains a significant global challenge due to its rising prevalence and severe complications, including cardiovascular diseases and chronic kidney disease. Advances in pharmacotherapy, particularly incretin-based treatments like GLP-1 receptor agonists and DPP-4 inhibitors, have transformed diabetes management. GLP-1 receptor agonists are highly effective in reducing HbA1c, promoting weight loss, and offering cardiovascular and renal protection, making them ideal for high-risk patients. DPP-4 inhibitors, while less potent, provide a safe and tolerable option for patients with mild hyperglycemia or chronic kidney disease, particularly older adults. A patient-centered approach that tailors therapy to individual needs ensures optimal outcomes. Future research should focus on long-term benefits and innovative treatment strategies to further enhance diabetes care and reduce its burden on patients and healthcare systems. [2,18]

Disclosures

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