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REVIEW ARTICLE
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A COMPARISON OF GLP-1 RECEPTOR AGONISTS AND DPP-4 INHIBITORS FOR THE TREATMENT OF DIABETES MELLITUS TYPE 2: A SYSTEMATIC REVIEW

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Abstract

Introduction: Decisions on balancing use of GLP-1 receptor agonists or DPP-4 inhibitors depend on various factors like patient's own characteristics and choice, in addition to medical background. GLP-1 receptor agonists and DPP-4 inhibitor are a class of medications that work on incretin system to normoglycemia.

Aims and Objectives: To compare the effectiveness of drugs for the treatment of type 2 diabetes: GLP-1 receptor agonists Vs DPP-4 inhibitors.

Methods: A search of the MEDLINE databases restricted to human clinical trials using the search terms 'GLP-1RA' or 'DPP-4 inhibitor' produced seven direct comparative studies and one post hoc analysis all comparing a GLP-1RA with sitagliptin. The effectiveness and safety of GLP-1RAs and DPP-4 inhibitors in T2D patients was assessed by use of a variety of tools including research studies, treatment algorithms, product prescribing information, and personal clinical experience.

Results: For GLP-1RAs, direct clinical trials showed superior control of blood sugar levels, weight reduction, and general drug approach compared to sitagliptin: the DPP-4 inhibitions through these medications, rarely, consumers experience side effects like nausea. However, with a proper education and threat, dosage increase could manage it, though. The nausea is momentarily. From a nutshell, the existing treatment guidelines make an increment over metformin medication with a switch to an incretin-based agent for further reducing the cardiovascular risk in those patients who are already on the treatment, but this use remains restricted in some countries.

Conclusion: GLP-1RAs give a better glucose control and weight loss in T2D than DPP-4 inhibitors. Alternatives are DPP-4 inhibitors instead of GLP-1RAs in situations of no prominent weight changes, when formulation by mouth is necessary or only well-tolerated GLP-1RAs are available.

Keywords: Diabetes, GLP-1, DPP-4, Blood sugar, Receptor.

INTRODUCTION

Diabetes mellitus (DM) is considered one of the oldest diseases in human history. . The fact that an Egyptian manuscript contained this record is approximately 3,000 years old **[1].**

In 1936, a critical distinction between type 1 and type 2 diabetes mellitus was made. In 1988, type 2 diabetes was first acknowledged as one of the conditions for metabolic syndrome **[2], [3].**

T2DM is a chronic condition that is one of the major public health problems worldwide. The estimate is that by year 2030 about 366 million people will suffer from Type 2 Diabetes Mellitus across the globe **[4].**

DM, standing for metabolic syndrome, is a very complex illness because of the fluctuations in blood glucose levels. The diabetes mellitus (DM) can be classified into two groups Type 1 Diabetes Mellitus (T1DM) and T2DM (T2DM).

T2DM is a disorder that is inflammatory in nature with a disordered immune system **[5], [6].**

In the clinical definition provided by the WHO, diabetes mellitus is a chronic metabolic disorder that is characterized by increased levels of blood glucose. It is this chronic and constant challenge to vital organs such as heart, blood vessels, eyes, kidneys, and nerves. T2DM, a worldwide spread condition classified above 90% of diabetes mellitus cases, is characterized by insulin secretion deficiency of pancreatic islet β-cells, IR of tissue and an inadequate compensatory insulin secretory response **[7], [8].**

T2DM's relentless advancement leads to inadequate insulin secretion, causing hyperglycaemia due to disrupted glucose balance. In the vast majority of T2DM patients, abdominal obesity or excess of body fat is among the most frequently encountered symptoms. Adipose tissue plays an important role in the development of insulin resistance due to the variety of inflammatory mechanisms that take place during a metabolic state. These hormone pathways are triggered mainly by FFA's increased release and the fall of adipokines resulting in insulin's dysfunction.

The current worldwide trends that are mostly deal with the increasing occurrence and frequency of the T2DM include the overwhelming prevalence of obesity, inactive lifestyles, consumption of high-calorie diet and the aging problem. The synergistic impact of these factors has brought the prevalence of T2DM about four times more than it used to be **[9], [10].**

GLP-1 receptor agonists

GLP-1 receptor agonists are gaining popularity not only as a selected treatment but also as a key component of the therapy for type 2 diabetes and obesity. These medications are similar to the GLP-1 (glucagon-like peptide 1) hormone, which is produced by the gastrointestinal tract and is responsible for helping to control glucose levels after meals. The modelling is most useful in reducing blood sugar level and weight loss for those patients who are suffering with diabetes and obesity.

GLP-1 receptor agonists offer more than blood sugar level regulation and weight control since they have effects that exceed their blood sugar regulating and weight control effects these agents have shown activities in reducing problem of cardiac and kidney complications in people with diabetes. GLP 1 agonists decrease cardiovascular morbidity and mortality by altering mechanisms like blood pressure and lipids. Moreover, their usage is linked to a reduced probability of hypoglycaemic events, a prevalent worry in diabetes care, providing a more advantageous safety profile compared to certain other ant diabetic drugs.

GLP-1 receptor agonists additionally possess a significant effect on reducing hunger. These medications help increase the sensation of fullness, aiding in appetite control, which supports weight loss and offers a comprehensive strategy for addressing issues related to obesity. These drugs are beneficial in treating individuals with both type 2 diabetes and obesity due to their impact on glucose metabolism and body weight.

While GLP-1 receptor agonists offer evident advantages, it is crucial to acknowledge that they also come with adverse effects. Commonly reported side effects associated with their use are nausea, vomiting, diarrhea, and injection site reactions. It is crucial to comprehend that these side effects are typically transient and diminish over time.

GLP-1 receptor agonists are typically given via subcutaneous injections, and the frequency of dosing is based on the specific medication. Some formulations necessitate daily injections, while others provide the convenience of weekly dosing, accommodating individual preferences and treatment adherence.

GLP-1 receptor agonists like "exenatide, liraglutide, dulaglutide, and semaglutide" have distinct pharmacokinetic profiles and clinical implications. Healthcare professionals can tailor treatment plans for patients with T2D and obesity using a range of options to enhance treatment effectiveness and patient satisfaction **[11], [12], [13].**

DPP-4 inhibitors

Gliptins, or dipeptidyl peptidase 4 (DPP-4) inhibitors, are essential drugs for controlling type 2 diabetes by lowering blood glucose levels. A number of cardiovascular complications, including heart failure, strokes, and coronary diseases, are significantly increased by this metabolic disorder.

Healthcare personnel who treat diabetic patients need to be well versed in DPP-4 inhibitor therapy.

The FDA has approved oral diabetic medications, such as sitagliptin, saxagliptin, linagliptin, and alogliptin, for the treatment of type 2 diabetes in adults. The FDA has not yet approved vildagliptin, despite being approved by the European Medicines Agency (EMA). The way that it works is by modifying incretin hormones, which are vital hormones of the gastrointestinal tract that regulate blood sugar levels after food is consumed orally.

Beyond their ability to lower blood glucose levels, DPP-4 inhibitors have a complex pharmacological profile. They show effects on blood vessels, kidneys, heart, and other vital organs that include immunomodulatory, antihypertensive, anti-inflammatory, and antiapoptotic. The fact that the aforementioned effects have nothing to do with the incretin pathway suggests that DPP-4 inhibitors have broader therapeutic applications.

Research suggests that this group of drugs may be advantageous for individuals who have undergone kidney and liver transplants and have developed new-onset diabetes after the procedure, known as NODAT, because of their multiple benefits. DPP-4 inhibitors are multifunctional and can be used alone or in conjunction with other drugs. When used in conjunction with medications like metformin, sulfonylureas, thiazolidinediones, or insulin, they offer a flexible and effective approach to managing blood glucose levels in patients with T2DM.

An inter-professional approach is essential for maximizing patient outcomes. Healthcare providers, such as physicians, nurses, dieticians, and pharmacists, work together to customize DPP-4 inhibitors therapy based on each patient's specific needs. Having a thorough understanding of the indications, contraindications, potential adverse events, and overall pharmacological effects of DPP-4 inhibitors is crucial for providing patient-centered care and effectively managing diabetes in various clinical situations **[14], [15], [16], [17], [18], [19], [20].**

AIMS and OBJECTIVES

In recent years, the diabetes treatment field has witnessed an increase in therapeutic options, with glucagon-like peptide-1 receptor agonists (GLP-1RAs) and dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) gaining popularity. Several clinical trials have extensively investigated the efficacy and safety profiles of these agents individually, typically in comparison to placebos or traditional oral anti-diabetic drugs (OADs). There is a notable lack of direct comparisons between GLP-1RAs and DPP-4 inhibitors, making it difficult for clinicians and healthcare providers to assess their comparative advantages.

This study aims to fill this gap by examining trials that directly compare GLP-1RAs and DPP-4 inhibitors. The main goal is to analyze detailed insights on the comparative effectiveness, safety, and

tolerability of these two different types of anti-diabetic medications. We aim to clarify the distinctive characteristics and potential benefits of each drug class by examining the details of these direct comparison trials.

Moreover, our study will investigate the broader clinical context to determine when one class may be more advantageous than the other, going beyond direct comparison. Various factors including patient characteristics, comorbidities, treatment goals, and personalized therapeutic considerations will be considered. We aim to offer clinicians a detailed framework to aid in decision-making, enabling the customization of diabetes management strategies.

The study will synthesize current evidence and evaluate the methodological aspects of the trials being considered. This will require a thorough examination of study designs, patient demographics, and outcome metrics to guarantee the validity and applicability of the results. We strive to provide strong insights through a thorough approach to inform clinical practice based on evidence and contribute to the development of diabetes management guidelines.

METHODOLOGY

A comprehensive search strategy was used to assess the safety and effectiveness of dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) and glucagon-like peptide-1 receptor agonists (GLP-1RAs) in people with type 2 diabetes (T2D). 'GLP-1RA' and 'DPP-4 inhibitor' were used to search the MEDLINE database methodically. The goal of this strategy was to locate clinical trials that directly contrasted the two classes of anti-diabetic drugs.

Nine pertinent studies were found in the search. One study was excluded from the analysis because it compared exenatide once weekly (OW) with sitagliptin as monotherapy. The exclusion was due to exenatide OW not being approved for use as monotherapy. The studies that were considered appropriate for inclusion served as the basis for our comparative analysis.

The efficacy and safety comparison was done by combining trial data with treatment algorithms, product information, and personal clinical experiences. This comprehensive approach ensured a thorough evaluation by taking into account evidence from rigorous clinical trials and practical considerations from real-world clinical settings.

The study seeks to uncover the subtle distinctions in the effectiveness of GLP-1RAs and DPP-4 inhibitors in various aspects such as glycemic control, weight management, cardiovascular outcomes, and safety profiles. Our analysis aims to offer clinician’s valuable insights into tailoring therapeutic strategies for patients with T2D by combining data from various sources to provide a comprehensive understanding of how these two classes of medications compare.

The presence of treatment algorithms and product prescribing information enables a contextualized understanding of the trial results. This method takes into account the wider scope of diabetes management by integrating guidelines and recommendations to place the study results within the context of current clinical practices.

RESULT AND DISCUSSION

There is limited research comparing GLP-1RAs and DPP-4 inhibitors directly. Sitagliptin is the sole DPP-4 inhibitor that has been compared to GLP-1RAs in studies. Although DPP-4 inhibitors may differ, head-to-head data from clinical trials offer a reliable assessment of the comparison between GLP-1RAs and DPP-4 inhibitors because of their comparable effectiveness **[21], [22].**

Two brief cross-over clinical trials, one lasting four weeks and the other eight weeks, have compared exenatide BID and sitagliptin (see Table 1). Exenatide BID outperformed sitagliptin in improving 24-hour and postprandial glucose levels in patients with uncontrolled type 2 diabetes receiving metformin therapy. There was a decrease in 2-hour postprandial glucose levels when exenatide BID was substituted for sitagliptin, but an increase in 2-hour postprandial glucose levels when exenatide BID was substituted for sitagliptin. Table 1 shows that compared to sitagliptin, exenatide BID treatment significantly slowed gastric emptying and decreased total daily caloric intake, leading to greater weight loss. Hypoglycemia was not significantly caused by either treatment. When comparing

exenatide to sitagliptin, the most common side effects were mild to moderate gastrointestinal problems (nausea, vomiting, diarrhea) **[23], [24].**

Table 1: Summary of study

Study	Duration (n)	Treatment	Change in glycaemic control	Change in body weight		
De Fronzo et al. [23]	2 weeks (61)	Exen BID + Met Switch 2 weeks (61)	2-h PPG: -6.2 mmol/l; p < 0.0001- Exen BID - Sita	-0.8 kg: p = 0.006* Sita + Met 2-h PPG: +4.1 mmol/l Sita Exen BID	2-h PPG: -2.1 mmol/l N/A 2-h PPG: -4.2 mmol/l	-0.3 kg N/A
Berg et al. [24] Bergenstal et al. [25]	4 weeks (86) 26 weeks (342)	Exen BID + Met/TZD Exen ow + Met	24-h glucose: -2.3 mmol/l; p < 0.001-2-h PPG: mmol/l; p < 0.001- HbA1c: -1.5%: p < 0.0001	-1.37 kg; p < 0.05- Sita + Met/TZD -2.3 kg: p = 0.0002 Sita + Met	24-h glucose: -1.6 mmol/12-h PPG: -2.5 mmol/l HbA1c: -0.9%	-0.89 kg -0.8 kg
Wysham et al. [26]	Switch 26 weeks(130)	Sita - Exen ow	HbA1c: -0.3%: p = 0.001	-1.1 kg: p = 0.0006+		
Pratley et al. [27]	26 weeks (665)	Lira 1.2 mg + Met	HbA1c: -1.24%: p < 0.0001 vs. Sita	-2.9 kg: p < 0.0001 VS. Sita Lira 1.8 mg + Met Sita + Met	HbA1c: -1.5% p < 0.0001 VS. Sita HbA1c: -0.9%	-3.4 kg; p < 0.0001 vs. Sita -1.0 kg
Pratley et al. [28]	52 weeks (665)	Lira 1.2 mg + Met	HbA1c: -1.29%: p < 0.0001 VS. Sita	-2.8 kg: p < 0.0001 vs. Sita Lira 1.8 mg + Met Sita + Met	HbA1c: -1.51%: p < 0.0001 vs. Sita HbA1c -0,88%	-3.7 kg: p < 0.0001 VS. Sita -1.2 kg
Pratley et al. [29]	Switch 26 weeks(419)	Sita - Lira 1.2 mg	HbA1c: -0.24%: p = 0.006	-1.64 kg: p < 0.0001 Sita - Lira 1.8 mg	HbA1c: -0.45% p = 0.0001	-2.48 kg: p < 0.0001

For the first week, Exenatide BID is administered at a dose of 5 μg twice daily; after that, it is increased to 10 μg twice daily. The recommended daily dosage of sitagliptin is 100 mg, to be taken once in the morning. As prescribed, exenatide OW should be taken once a week in a dose of 2 mg. The dosage of ligarglutide is administered gradually: 0.6 mg once daily for the first two weeks, then 1.2 mg once daily for the next two, and 1.8 mg at week four if needed.

"Abbreviations: BID (twice daily), Exen (exenatide), Met (metformin), N/A (data not available), PPG (postprandial glucose), OD (once daily), OW (once weekly), Sita (sitagliptin), and TZD (Thiazolidinedione)."

- Comparative treatment group
- Compared to the baseline (pre-switch) value.

A 26-week randomized trial compared Exenatide OW with sitagliptin in patients with inadequately controlled type 2 diabetes who were only taking metformin. The trial showed significant benefits of Exenatide OW, with notable decreases in HbA1c and body weight compared to sitagliptin, as detailed in Table 1. No significant cases of hypoglycemia were reported, and the main adverse events for both treatments were associated with the gastrointestinal system.

Table 1 demonstrates the comparative results, highlighting the effectiveness of Exenatide OW in enhancing glycemic control and promoting weight loss in this particular group of patients. The results indicate that Exenatide OW could be a beneficial option for patients with poorly managed type 2 diabetes who are taking metformin.

Furthermore, in the following 26-week study extension, patients who were initially taking sitagliptin changed to Exenatide OW. This change led to additional and statistically significant decreases in both HbA1c levels and body weight, as outlined in Table 1. The study extension highlights the continued and advantageous effects of Exenatide OW, even when patients switch from another antidiabetic medication. Exenatide OW has a favorable profile in managing type 2 diabetes due to the lack of significant hypoglycemia cases and the continued occurrence of gastrointestinal events as the most common adverse events. The results provide valuable information on the effectiveness of Exenatide OW as a strong treatment choice for patients with poorly managed type 2 diabetes, especially when used in combination with metformin **[25], [26].**

A 26-week randomized trial was conducted to assess the safety and effectiveness of liraglutide at doses of 1.2 mg and 1.8 mg compared to sitagliptin in patients with uncontrolled type 2 diabetes who were also taking metformin. The detailed analysis in Table 1 revealed that combining liraglutide with sitagliptin resulted in significant reductions in HbA1c levels and body weight for both the 1.8 mg and 1.2 mg doses.

Minor hypoglycemia was rare, occurring in only 5% of cases in all study groups. Furthermore, although liraglutide usage led to a greater occurrence of nausea, it was temporary. The results highlight the positive safety record of liraglutide when combined with metformin, offering confidence in the controllable nature of the reported side effects.

Regardless of the starting HbA1c levels, liraglutide at doses of 1.2 mg and 1.8 mg consistently lowered HbA1c levels more effectively than sitagliptin. This indicates that liraglutide may provide improved and consistent management of blood sugar levels in individuals with uncontrolled type 2 diabetes, regardless of their initial blood sugar levels.

The study investigated the long-term sustainability of the positive results by incorporating a 26-week extension phase, during which 419 patients switched from sitagliptin to liraglutide (at doses of 1.2 mg or 1.8 mg). The improvements in HbA1c and body weight achieved during the first 26 weeks were sustained and continued to show significant improvement. The long-lasting effectiveness of liraglutide demonstrates its lasting advantages as a treatment for people with uncontrolled type 2 diabetes, particularly when switching from other antidiabetic drugs **[28], [29], [30].**

GLP-1RAs consistently show superior efficacy in reducing blood glucose levels and promoting greater weight loss compared to sitagliptin, as indicated by the trial results. Both drug categories have a low likelihood of causing hypoglycemia, which is consistent with our knowledge of how they work. Yet, this needs to be balanced with the requirement for GLP-1RAs to be given through injection and their increased tendency to induce nausea, especially at the beginning of treatment.

An analysis of data from the LIRA-DPP-4 and LEAD-6 studies suggests that using liraglutide 1.8 mg early on could be a viable option instead of sitagliptin as additional treatment to metformin in patients with near-target HbA1c levels (> 8.0% or 63.9 mmol/mol). After 26 weeks of treatment, liraglutide showed a significantly greater reduction in HbA1c compared to sitagliptin (-1.01% vs. -0.48%; $p < 0.0001$). More than double the amount of patients reached HbA1c targets with liraglutide 1.8 mg compared to the control group. The differences were statistically significant ($p < 0.0001$) for both HbA1c < 7.0% and HbA1c ≤ 6.5%. Moreover, a higher number of patients achieved HbA1c goals with liraglutide 1.8 mg than with exenatide BID [HbA1c < 7.0% (53.0 mmol/mol): 84% vs. 62%, $p = 0.03$; HbA1c ≤ 6.5% (47.5 mmol/mol): 65% vs. 35%, $p = 0.01$] **[31].**

Patient selection: guidelines and future trends

Clinical guidelines are crucial in directing healthcare professionals on how to make well-informed decisions regarding the most effective management of T2D. These guidelines are essential tools that offer evidence-based recommendations based on up-to-date data. These guidelines are periodically updated to ensure that healthcare practices are in line with the most recent scientific knowledge as new therapeutic options become available in the evolving landscape of diabetes management. Esteemed organizations like the AACE and the ADA/EASD play a significant role in developing these guidelines. These organizations create detailed algorithms that provide systematic methods for handling Type 2 Diabetes. The AACE stresses the significance of customizing treatment according to initial HbA1c levels and offers a comprehensive algorithm that classifies 11 primary medication groups and treatment strategies. Local guidelines, like those from the National Institute for Health and Clinical Excellence (NICE) in England and Wales, are essential for healthcare decision-making. NICE guidelines assess the cost-effectiveness of medications in addition to clinical efficacy, prompting healthcare providers to consider both clinical outcomes and economic factors when choosing treatments. The AACE's diabetes management algorithm is highly detailed, organizing treatment methods according to three initial HbA1c levels. The AACE recommends metformin as the initial treatment for monotherapy when HbA1c levels are higher than 7.5% or 58.5 mmol/mol, followed by GLP-1RAs. GLP-1RAs are recommended over DPP-4 inhibitors for dual/triple therapy when HbA1c is 7.5% or higher. When HbA1c levels exceed 9.0% or 74.9 mmol/mol, indicating the necessity for dual, triple, or insulin therapy, GLP-1RAs are given priority, highlighting their effectiveness in advanced stages of T2D. The AACE algorithm emphasizes a preference for GLP-1RAs over DPP-4 inhibitors in patients on basal insulin needing better control of post-meal blood

sugar levels. This subtle approach highlights the significance of customizing treatment strategies based on the unique needs and characteristics of each patient. The EASD/ADA position statement recommends GLP-1RAs or DPP-4 inhibitors as alternatives if metformin alone is not effective, offering a different view on the order of treatment options **[32], [33].**

The NICE offers detailed guidance on managing Type 2 Diabetes (T2D), providing specific recommendations tailored to each patient's characteristics and clinical factors. If metformin alone is not effective, indicated by HbA1c level of ≥ 6.5% (47.5 mmol/mol), NICE recommends using DPP-4 inhibitors as a second-line treatment. This advice is especially relevant when sulfonylureas (SU) are not recommended, not well received, or carry a high risk of hypoglycemia or its complications. NICE emphasizes the significance of customizing treatment approaches based on individual patient requirements and possible issues. NICE recommends giving priority to using GLP-1RAs when significant concerns about body weight or weight-related conditions are the focus. This strategic approach is in line with the increasing acknowledgment of the importance of weight factors in managing diabetes. NICE recommends adding liraglutide 1.2 mg and exenatide BID to metformin and sulfonylurea/thiazolidinedione (SU/TZD) in cases where triple therapy is needed. This comprehensive strategy recognizes the various ways in which these medications work, with the goal of improving blood sugar regulation while taking into account each patient's specific needs. NICE recommends prioritizing weight loss interventions for patients with HbA1c levels over 7.5%, BMI of 35 kg/m2 or higher and facing psychological or medical issues due to increased body weight. This focus on personalized care demonstrates a holistic view, acknowledging the interrelation between metabolic health and overall well-being. NICE recognizes the benefits of weight loss, not just for controlling blood sugar levels but also for reducing other health conditions related to obesity. This applies to individuals with a BMI below 35 kg/m2, emphasizing the importance of weight control in the context of T2D **[34], [35].**

Both the EASD/ADA position statement and the AACE consensus guidelines recommend using incretin-based therapies, especially GLP-1RAs, frequently when metformin is not effective. Clinicians should adhere to local guidelines recommending the prioritization of incretin-based therapies for specific patient populations **[36], [33].**

DPP-4 inhibitors and GLP-1RAs: contraindications, safety concerns and special populations

Contraindications: Contraindications for DPP-4 inhibitors and GLP-1RAs, such as exenatide BID and lixisenatide, are related to hypersensitivity to any of their components. Avoid using these medications if you are allergic or hypersensitive to any of their ingredients. This measure is essential to avoid negative responses that can vary from minor to serious. Exenatide OW and liraglutide in the United States have additional contraindications for individuals with a personal or family history of medullary thyroid carcinoma or those diagnosed with multiple endocrine neoplasia syndrome type 2 (MEN-2). These circumstances increase the risk, and administering these drugs in such situations could worsen the health problems linked to thyroid carcinoma or MEN-2. Clinical trials of DPP-4 inhibitors have not shown an increased incidence of skin lesions. The evidence is inconclusive regarding a potential link, despite some post-marketing reports and case studies. Due to limited data on diabetic skin complications linked to DPP-4 inhibitors, healthcare providers should carefully observe patients prescribed these medications for any indications of skin issues. Being vigilant is crucial to ensuring the safety and well-being of individuals using DPP-4 inhibitors. GLP-1RAs have been associated with uncommon adverse events, such as reactions affecting the skin and tissues. Although rare, healthcare professionals should be mindful of the possibility of these reactions. It is essential to monitor for any abnormal skin symptoms or tissue-related problems while undergoing treatment with GLP-1RAs. The infrequency of these occurrences highlights the necessity of ongoing monitoring and immediate intervention upon detection of any negative reactions **[37], [38], [39], [40], [41], [42], [43], [44], [45], [46], [47], [48], [49], [50].**

Pancreatitis and pancreatic cancer: Extended use of GLP-1 receptor agonists (GLP-1RAs) and dipeptidyl peptidase-4 (DPP-4) inhibitors has been associated with possible risks of pancreatitis. Prolonged use of these antidiabetic medications may lead to histological alterations that could elevate the risk of chronic pancreatitis, potentially increasing the likelihood of pancreatic cancer. Healthcare providers need to be cautious about these risks when considering the extended use of these medications. In the Phase 3 clinical trial of liraglutide, there was a slightly higher incidence of pancreatitis compared to the control group, but it remained below the anticipated rate in a general population with type 2 diabetes (T2D). This emphasizes the importance of continuously monitoring and evaluating pancreatic health in individuals undergoing treatment with GLP-1RAs. DPP-4 inhibitors like sitagliptin, vildagliptin, saxagliptin, and exenatide BID have been linked to instances of acute pancreatitis in post-market data. If pancreatitis is suspected, it is recommended to discontinue both DPP-4 inhibitors and GLP-1RAs promptly as a precautionary measure. An inquiry into the pancreatic safety of incretin therapies was initiated following a report suggesting an increased risk of potentially precancerous pancreatic mass in patients using sitagliptin or exenatide BID. Thorough analysis of these results is crucial due to the methodological flaws present in the study. Significant disparities were noted between the two cohorts of diabetic patients, especially regarding age and gender distribution. The control group participants were younger on average and had a higher percentage of females than the treated group. Additionally, there were concerns about the influence of participants with type 1 diabetes in the control group, as this condition is associated with a decrease in pancreatic mass within ten years of diagnosis. An editorial in a medical journal questioned whether the observed increase in pancreas mass in patients receiving incretin-based therapy was due to the treatment or influenced by factors such as the presence of individuals with type 1 diabetes in the control group. This type of diabetes is associated with a progressive reduction in pancreatic mass. The FDA recommended patients and healthcare providers to continue their current treatment, while the European Medicines Agency determined that the data on GLP-1-based treatments did not indicate an increased risk of pancreatic side effects after a thorough review **[37], [38], [39], [40], [41], [42], [43], [44], [45], [46], [47], [48], [49], [50], [51], [52], [53], [54], [55].**

Cardiovascular outcome studies involving approximately 11,000 subjects treated with DPP-4 inhibitors have recently been published for alogliptin and saxagliptin combined. A low incidence of pancreatitis and pancreatic cancer was reported in both the SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction) and EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin vs. Standard of Care) randomized, double-blind, placebo-controlled clinical trials. Comparable rates were seen in both the active treatment and placebo groups **[56], [57].**

Renal insufficiency and acute renal failure:

Type 2 diabetes often leads to renal insufficiency, which can increase the levels of medications in the bloodstream and complicate treatment. GLP-1RAs have been linked to infrequent cases of acute renal failure. Acute renal failure caused by DPP-4 inhibitors is extremely uncommon. Evidence suggests that patients with T2D and renal issues may experience drug accumulation of sitagliptin, saxagliptin, and vildagliptin due to the kidneys being the main organs responsible for eliminating these medications. Dose adjustments are required when treating patients with moderate-to-severe renal impairment using sitagliptin, saxagliptin, and vildagliptin in the US and EU. Linagliptin is mainly eliminated through non-renal pathways, allowing it to be given at any point during renal disease treatment without requiring a dosage adjustment.

Whether taken once the kidneys mostly excrete weekly or twice daily, esomeatide, so people with severe renal impairment should avoid using it. For moderate to severe renal impairment, lixisenatide can be prescribed at the same dose; however, for more severe cases, there is not enough information available, so caution or avoidance is advised. Due to its similar metabolism to large proteins and lack of renal excretion, ligarglutide is cautiously approved for use in all stages of renal disease in the United States. Due to insufficient data, it is not advised in the EU for patients with moderate-to-severe

disease. The effect of incretin-based treatments on kidney function is currently being evaluated in multiple large prospective trials **[37], [38], [39], [41], [43], [44], [44], [42], [45], [46], [47], [48], [49], [58], [59], [60], [61], [62].**

When choosing whether to administer drugs such as GLP-1RAs and DPP-4 inhibitors to the elderly (≥ 75 years old), pediatric patients (< 18 years old), women who are pregnant or nursing, and people who have liver impairment, take into account the limited data that is currently available **[37], [38], [39], [40], [41], [42], [43], [44], [45], [46], [47], [48], [49].**

When incretin choice may be subjective or based on patient choice:

At first, doctors typically prefer to prescribe DPP-4 inhibitors rather than GLP-1RAs when a patient's HbA1c is within 1.5% of the target. The ease with which DPP-4 inhibitors can be incorporated into existing treatment plans and their lower cost are the primary reasons for this preference. Physicians need to take into account that the clinical studies reported that using DPP-4 inhibitors, together or with metformin treatment, usually led to HbA1c drop of less than 1%. Whether the patient is ready to lose weight or is sticking to the diet plan is an important pre-incretin therapy selection for patients who are close to achieving their weight loss target. The study showed a slight decrease in HbA1c among overweight or obese T2D individuals. Therefore, it might be appropriate for this group to use a GLP-1 Receptor Agonist that may confer future benefits of weight loss. Patients with heart failure who face substantial weight loss, according to some past researches, are more likely to have a higher mortality risk. Consequently, obese heart failure patients on GLP-1RAs should be subject to more frequent monitoring than the rest. DPP-4 inhibitors are a preferable choice for these patients as they do not cause substantial weight reduction compared to other medications **[22], [27], [63], [64], [65], [66].**

Due to its superior glycemic efficacy, particularly in overweight patients, a GLP-1RA is typically favoured over a DPP-4 inhibitor when patients with significantly poor glycemic control on oral anti-diabetic drugs (OADs) are more than 1.5% away from their target. If some patients do not have a positive response to GLP-1RA therapy, a DPP-4 inhibitor is often the next recommended treatment.

Dealing with practical issues: injections and gastrointestinal tolerability:

Compared to GLP-1RAs, DPP-4 inhibitors offer several advantages, mainly because they are easier to take orally and cause less nausea. Nausea is common during the early stages of GLP-1RA therapy and can be minimized by gradually increasing the dosage. A single 2 mg dose of exenatide OW is needed, but stable plasma levels take 6–10 weeks to achieve. Some patients may find relief from injecting GLP-RAs during meals. Based on first-hand experiences, liraglutide-induced nausea may be managed with strategies such as consuming smaller meals and stopping when satisfied. Sometimes after eating, patients may experience nausea that could be mistaken for satiety. One useful tactic for treating nausea is to lower the GLP-1RA dosage for a week and then gradually increase it back. Practitioners can demonstrate to patients who are hesitant to receive injections how easy and painless using GLP-1RA injection pens can be. The patient and the physician can both learn this point from a well-executed 'dry' injection. Furthermore, based on personal experiences, patients often find comfort in the fact that, when their eyes are closed, they can often barely distinguish between a gentle pinch on the arm and a dry needle **[38], [39], [43], [41], [42].**

Findings from research on patient-reported outcomes indicate that when injectable therapies offer advantages over oral treatments, patients are happy with them. Studies show that while sitagliptin and liraglutide 1.8 mg are rated similarly for convenience and flexibility, patients are noticeably more satisfied with the former. After 26 weeks of treatment, exenatide OW exhibits better overall treatment satisfaction than sitagliptin. When liraglutide is substituted for sitagliptin, treatment satisfaction is generally higher, particularly when liraglutide 1.2 mg is used. This is because different administration methods do not compromise treatment convenience or flexibility. In these situations, improved glycemic control and more weight loss are linked to GLP-1RA treatment satisfaction as opposed to sitagliptin therapy **[67], [68], [29].**

These findings suggest that both treatment efficacy and convenience are equally important for patients. Patients are satisfied with an injectable therapy if it provides extra clinical advantages.

CONCLUSION

When used in conjunction with metformin treatment, incretin-based therapies that are well known for improving glycaemic control with a low risk of hypoglycemia and without causing weight gain—represent a superior option than conventional supplements. When metformin ± SU is not working, DPP-4 inhibitors, a well-known member of this class, are frequently easily added to the current treatment plan. Interestingly, these inhibitors have the benefit of little weight gain and few gastrointestinal adverse effects.

However, when compared to sitagliptin, GLP-1RAs—a different class of incretin-based therapies—show better blood sugar control and weight loss. This is because they provide higher levels of GLP-1RA, as opposed to GLP-1 and GIP, which sitagliptin achieves. GLP-1RAs are easier to administer than DPP-4 inhibitors, and giving a patient their first injection in a medical setting helps reduce needle anxiety.

Patient satisfaction data indicates that GLP-1RA is preferred over sitagliptin, and patients are frequently open to switching from oral to injectable medication in the hopes of experiencing increased efficacy. Personally, I think GLP-1RA should be used instead of DPP-4 inhibitors. However, a DPP-4 inhibitor might be considered appropriate in situations where achieving glycemic targets only requires a slight decrease in HbA1c and weight loss is not a top priority.

It is interesting to note that in some patient populations, especially those with obesity-related medical conditions, GLP-1RAs are typically preferred over DPP-4 inhibitors. Promoting the early use of GLP-1RAs during the course of the disease may lead to better blood sugar regulation and ensuing weight loss, which may ultimately improve long-term results.

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