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**Practical guide for using glucagon-like peptide-1 and dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonists for the management of type 2 diabetes mellitus**

Alqifari SF *et al.* GLP-1 and dual GIP and GLP-1 RAs

## Abstract

In 2005, exenatide became the first approved glucagon-like peptide-1 receptor agonist (GLP-1 RA) for type 2 diabetes mellitus (T2DM). Since then, numerous GLP-1 RAs have been approved, including tirzepatide, a novel dual glucose-dependent insulintropic polypeptide (GIP/GLP-1 RAs), which was approved in 2022. This class of drugs is considered safe with no hypoglycemia risk, making it a common second-line choice after metformin for treating T2DM. Various considerations can make selecting and switching between different GLP-1 RAs challenging. Our study aims to provide a comprehensive guide for the usage of GLP-1 RAs and dual GIP and GLP-1 RAs for the management of T2DM.

**Key Words:** Glucagon-like peptide-1 receptor agonist; Diabetes mellitus; Metabolic syndrome; Dual glucose-dependent insulintropic polypeptide and glucagon-like peptide-1 receptor agonist; Clinical practice; Endocrinology

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**Core Tip:** Various glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are available for the management of type 2 diabetes mellitus including short-acting and long-acting injectables as well as one agent as an oral tablet. Furthermore, dual glucose-dependent insulintropic polypeptide (GIP) and GLP-1 RA have now emerged as the newest addition to the long-acting injectables selection. With the availability of various options, the complexity of choosing, titrating, and switching between agents, especially in certain patient populations, has become increasingly challenging. We aim to provide a

comprehensive practical clinical guide for practitioners regarding GLP-1 RAs and dual GIP and GLP-1 RA use in everyday clinical practice.

## INTRODUCTION

<sup>15</sup> The glucose-dependent insulintropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) are hormones that are secreted in the intestine within minutes in response to food intake and are collectively known as incretin hormones<sup>[1]</sup>. They lower glucose levels and maintain a state of glucose homeostasis by enhancing insulin secretion following meals as well as by increasing the cells' sensitivity to insulin<sup>[2,3]</sup>. Additionally, they delay gastric emptying, leading to a sense of satiety, thus contributing to reduced food intake<sup>[4]</sup>.

Therefore, research focused on developing drugs that simulated the action of these hormones. In 2005, exenatide became <sup>7</sup> the first GLP-1 receptor agonist (GLP-1 RA) to be approved for the treatment of type 2 diabetes mellitus (T2DM)<sup>[5]</sup>. Later, more GLP-1 RAs were approved, and they showed good results in improving glycemic control and reducing weight<sup>[6,7]</sup>. Given its proven efficacy in weight reduction, liraglutide was approved in 2021 as a treatment for obesity, making it the first GLP-1 RA approved in that domain<sup>[8]</sup>. Moreover, tirzepatide is a novel drug with the dual effect of both GIP and GLP-1 RA actions which has been recently approved for treating T2DM<sup>[9]</sup>. It is available as a weekly subcutaneous injection and has shown positive results in controlling glucose levels and lowering the glycated hemoglobin level (HbA1C) as compared to other medications<sup>[10-12]</sup>.

<sup>16</sup> According to the recent recommendations by the American Diabetes Association/European Association for the Study of Diabetes and the American Association of Clinical Endocrinology, there is an agreement to consider GLP-1 RAs as a second-line therapy for patients with T2DM who did not show improvement with metformin<sup>[13-16]</sup>. The addition of GLP-1 RAs is also recommended for prediabetic patients for whom a normoglycemic state has not been achieved with lifestyle changes and/or metformin monotherapy<sup>[16]</sup>. Likewise, for patients with an initial HbA1C level <

7.5% as well, GLP-1 RAs are recommended as a second-line agent<sup>[16]</sup>. On the other hand, for patients with an entry HbA1C level 7.5%, a strategy of dual therapy including GLP-1 RAs as a first-line in addition to metformin is recommended<sup>[15]</sup>. GLP-1 RAs, along with sodium-glucose cotransporter 2 inhibitors, are considered the first-line add-on drugs in diabetic patients who have cardiovascular risk or chronic kidney disease<sup>[13-15]</sup>. Furthermore, GLP-1 RAs are indicated as a first-line intervention when metformin is contraindicated<sup>[13-15]</sup>. GLP-1 RAs are recommended due to their ability to enhance weight loss, lower the risk of hypoglycemia, provide cardiovascular and kidney-protective benefits, and reduce the incidence of microvascular complications of T2DM<sup>[13,14-18]</sup>.

Several GLP-1 RAs are available, each with varying characteristics, such as route of administration, frequency, dosing, cost, and dosage. Several factors may necessitate a healthcare professional to switch between different GLP-1 RAs. Recent literature indicates that there is a need for more information regarding specific GLP-1 RAs and dual GIP/GLP-1 RAs (*e.g.*, tirzepatide). Therefore, this protocol aims to fill these gaps by providing comprehensive guidance for the utilization of GLP-1 RAs and dual GIP/GLP-1 RAs. Specifically, we aim to develop clear practical guidance that will enable healthcare professionals to know how and when to utilize and switch between GLP-1 RAs and dual GIP/GLP-1 RAs.

## **LITERATURE REVIEW**

We searched PubMed using the terms GLP-1 AND (switch OR switching OR switched); and GLP-1 AND (once-daily OR “once daily”) AND (once-weekly OR “once weekly”) AND GIP AND dual GIP and GLP-1 with no lower limit set for the date, using MeSH and free text terms to match relevant articles. We included full text as text availability and all types of articles with publication dates starting from September 2003 to September 2023. We restricted the search to human studies and only those that were in the English language. These searches yielded 58, 78, and 25 results respectively. Abstracts of literature thus retrieved were then manually reviewed by two experts to

identify the relevant articles on utilization and switching between different GLP-1 RAs and dual GIP/GLP-1 RAs.

## **AN OVERVIEW OF GLP-1 AND DUAL GIP AND GLP-1 RA**

### *Characteristics and clinical implications*

GLP-1 RAs and dual GIP/GLP-1 RAs available in the market exhibit many similarities and variations. Despite being in the same class, GLP-1 RAs vary according to their pharmacological characteristics, effectiveness, and safety profiles<sup>[21-27]</sup>. GLP-1 RAs and dual GIP/GLP-1 RAs commonly available are listed in Table 1.

GLP-1 RAs showed efficacy in T2DM and obesity management<sup>[19-26]</sup>. The native intrinsic forms of human GLP-1 RAs have a very short half-life as dipeptidyl peptidase-4 degrades them rapidly after just a few minutes of being released into the bloodstream<sup>[27]</sup>. Consequently, structural modifications were made by removing amino acids or adding fatty acid chains to confer resistance to enzymatic degradation<sup>[27]</sup>.

A newly synthesized analog, tirzepatide, which has a dual agonism on GLP-1 and GIP receptors has been developed. It has a unique structure as a linear peptide with a fatty di-acid chain attached to it<sup>[28]</sup>. This novel compound has been found to significantly improve glycemic control and manage inadequate response in patients receiving insulin glargine<sup>[29]</sup>.

Most of the newly developed GLP-1 RAs can be administered subcutaneously *via* injections, except for the short form of semaglutide that is given orally. Exenatide is a short-acting agent taken in two daily doses, while oral semaglutide, lixisenatide, and liraglutide are all given once daily. Based on their extended half-life, the remaining medications are prescribed once-weekly<sup>[20-26]</sup>.

**Characteristics of semaglutide:** Semaglutide, a once-weekly injectable medication categorized as a specific GLP-1 RA has gained approval for managing T2DM at dosages of up to 1 mg. Clinical studies conducted on individuals receiving semaglutide revealed



significant average decreases in HbA1C of up to 1.8% and substantial average reductions in body weight of up to 6.5 kg<sup>[30]</sup>.

**Characteristics of tirzepatide:** Tirzepatide, a unique dual-action agent, functions both as a GIP and a GLP-1 RA and is a medication newly approved by the United States Food and Drug Administration (FDA) for managing T2DM. Its chemical structure is predominantly derived from the amino acid sequence of GIPs and incorporates a C20 fatty di-acid component<sup>[31]</sup>. Tirzepatide has an approximate bioavailability of 80%, and the time it takes to reach its highest concentration in the bloodstream can vary, spanning from 8 to 72 h, while its average apparent steady-state volume of distribution is roughly 10.3 liters. It is important to note that tirzepatide exhibits high binding to plasma albumin, with approximately 99% of the drug being plasma protein bound in the bloodstream. Upon injection, the peptide structure undergoes a proteolytic cleavage, marking the degradation and metabolism process of the drug. The C20 fatty di-acid component also experiences beta-oxidation and amide hydrolysis<sup>[31,32]</sup>. Tirzepatide has a half-life of 5 d, which enables dosing on a once-weekly basis. It is eliminated from the body as metabolites through urine and feces. Tirzepatide is administered through subcutaneous injection and is not currently available in oral form. It is available in several dosage options: 2.5 mg/0.5 mL, 5 mg/0.5 mL, 7.5 mg/0.5 mL, 10 mg/0.5 mL, 12.5 mg/0.5 mL, and 15 mg/0.5 mL. The starting dose is 2.5 mg for treatment initiation not intended for glycemic control and titrated to 5 mg after four weeks<sup>[31]</sup>.

In a 40-wk clinical trial involving 917 individuals diagnosed with T2DM comparing tirzepatide to insulin glargine, it was observed that tirzepatide led to a greater average reduction in HbA1C levels compared to insulin glargine. Furthermore, a smaller percentage of patients experienced hypoglycemia, defined as glucose levels below 54 mg/dL, when using tirzepatide as opposed to insulin glargine<sup>[32]</sup>. Moreover, there was a mean reduction in body weight of 5 kg, 7 kg, and 7.2 kg for individuals taking 5 mg, 10 mg, and 15 mg of tirzepatide, respectively<sup>[32]</sup>. Tirzepatide does not appear to elevate

the risk of major cardiovascular events. For instance, a meta-analysis of seven phase II and III trials comparing tirzepatide to either a placebo or an active comparator showed no increase in the composite cardiovascular endpoints associated with tirzepatide<sup>[32]</sup>.

Regarding the tirzepatide age threshold, the SURPASS 1-5 study distribution varied due to distinct inclusion and exclusion criteria with no upper age limit specified for participants. In the combined dataset from seven clinical trials, 30.1% of the patients who received tirzepatide were aged 65 years or older, and 4.1% were 75 years or older at the beginning of the study. Overall, there were no significant differences in terms of safety or effectiveness observed between the older patients and their younger counterparts. However, it is important to note the possibility that some older individuals may exhibit heightened sensitivity to the treatment cannot be definitively ruled out<sup>[26]</sup>. Additionally, as the SURPASS 1-5 trials excluded individuals under 18 years of age, a separate trial (NCT05260021) is set to assess the effects of tirzepatide in pediatric and adolescent participants aged 10 to 18 years who have type 2 diabetes<sup>[33]</sup>.

**Comparison of tirzepatide with semaglutide:** In a recent trial, tirzepatide, administered at doses of 5 mg, 10 mg, or 15 mg, exhibited noninferiority and superiority in comparison to injectable semaglutide at a dose of 1 mg. Tirzepatide reduced the HbA1C in patients diagnosed with T2DM who were also taking metformin as part of their treatment regimen<sup>[31]</sup>. The reductions in body weight were more significant in patients treated with tirzepatide when compared to those receiving injectable semaglutide. There was a difference of -1.9 kg, -3.6 kg, and -5.5 kg for tirzepatide at doses of 5 mg, 10 mg, and 15 mg, respectively, compared to injectable semaglutide<sup>[31]</sup>. Dual GIP/GLP-1 RA therapy seems to lead to more significant weight loss compared to GLP-1 RA alone. In a 40-wk clinical trial that compared tirzepatide with semaglutide, both administered once-weekly *via* subcutaneous injection, it was observed that tirzepatide resulted in a greater average reduction in body weight when compared to semaglutide<sup>[31,34]</sup>.



In the same study, among patients with T2DM, it was found that tirzepatide achieved a superior reduction in HbA1C levels compared to semaglutide<sup>[31]</sup>. In patients who were administered tirzepatide, the risk of hypoglycemia (defined as a blood glucose level below 54 mg per deciliter) was reported as 0.6%<sup>19</sup> in the 5-mg group, 0.2% in the 10-mg group, and 1.7% in the 15-mg group. In contrast, the risk of hypoglycemia was observed in 0.4% of individuals who received 1 mg of injectable semaglutide<sup>[31]</sup>. The most frequent adverse events reported were related to the gastrointestinal (GI) system and were generally of mild to moderate severity in both the tirzepatide and injectable semaglutide groups. Specifically,<sup>3</sup> nausea was reported in 17% to 22% of patients treated with tirzepatide and in 18% of those receiving semaglutide. Diarrhea was reported by 13% to 16% of tirzepatide-treated patients and 12% of those taking semaglutide. Vomiting was experienced by 6% to 10% of tirzepatide recipients and 8% of semaglutide recipients, while a reduced appetite was noted in 7% to 9% of tirzepatide-treated patients and 5% of those on 1 mg semaglutide. In another trial comparing tirzepatide with semaglutide, the incidence of adverse GI effects was similar between the two groups<sup>[31,33]</sup>.<sup>3</sup> Serious adverse events were documented in 5% to 7% of patients receiving tirzepatide and in 3% of those taking injectable semaglutide. Hypersensitivity reactions were observed<sup>3</sup> in 1.7% to 2.8% of patients treated with tirzepatide and in 2.3% of those treated with semaglutide. Injection-site reactions were reported in 1.9% to 4.5% of patients receiving tirzepatide and 0.2% of those receiving semaglutide. Notably, these injection-site and hypersensitivity reactions were generally of mild to moderate severity, and no severe cases of either were reported<sup>[31,34]</sup>.

#### *Interactions of dual GIP and GLP-1 RAs with other medications*

Drug interactions can significantly impact the effectiveness and safety of drug therapy. The therapeutic efficacy of tirzepatide can be increased when used in combination with insulin secretagogues such as sulfonylureas or insulin and oral antidiabetic agents. Nevertheless, this combination also leads to a higher risk of hypoglycemia.

GLP-1 RAs slow down gastric emptying, which may induce pharmacokinetic changes in interacting drugs such as acetaminophen, digoxin, warfarin, oral contraceptives, metformin, statins, angiotensin-converting enzyme inhibitors, and griseofulvin. Despite these interactions, they are generally deemed clinically insignificant, and dosage adjustments are unnecessary when using most of these drugs concurrently with GLP-1 Ras<sup>[35]</sup>. However, it is important to note that the simultaneous administration of warfarin with GLP-1 RAs may result in an increased international normalized ratio (INR), and although this effect is not significant, close monitoring of the INR is advised considering warfarin's narrow therapeutic index<sup>[36]</sup>. Furthermore, to avoid any delay in drug absorption, it is recommended to take interacting drugs approximately 1 h before administering GLP-1 Ras<sup>[36]</sup>.

#### *The cardioprotective effect of dual GIP and GLP-1 RAs*

GLP-1 RAs provide cardioprotective effects through several mechanisms. These agents lower systolic blood pressure by around 2-3 mmHg, reduce endothelial inflammation and oxidative stress, and promote the induction of endothelial nitric oxide synthase, which increases nitric oxide availability<sup>[37]</sup>. Additionally, GLP-1 RAs promote natriuresis and diuresis by inhibiting the sodium-hydrogen exchanger 3 of the renal proximal tubular cells, which could partly account for the blood pressure-lowering effects<sup>[38]</sup>.

GLP-1 RAs display anti-inflammatory properties by reducing the production of proinflammatory cytokines such as tumor necrosis factor- $\alpha$ , interleukin (IL)-6, and IL-1 $\beta$  and the C-reactive protein levels<sup>[42,43]</sup>. Furthermore, GLP-1 RAs decrease the expression of adhesion molecules (specifically vascular cellular adhesion molecule-1, intercellular adhesion molecule-1, and P-selectin) on the endothelial cell surfaces, consequently reducing adhesion and migration of inflammatory cells, particularly monocytes and neutrophils through the vascular wall, which reduces the formation of atherosclerotic plaque<sup>[39]</sup>. Moreover, GLP-1 RAs demonstrated anti-aggregation effects on the activity of murine and human platelets in numerous preclinical studies<sup>[40]</sup>.

### *Cardiovascular outcome trials of dual GIP and GLP-1 RAs*

Due to the strong association between T2DM and cardiovascular complications, clinical studies must establish the cardiovascular safety of any drug for T2DM to obtain United States FDA approval. This has led to many cardiovascular outcome trials involving innovative glucose-lowering medications like GLP-1 RAs.

<sup>9</sup> The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial assessed the cardiovascular safety of liraglutide in 9340 patients with T2DM and high cardiovascular risk. Participants were randomly assigned to receive either 1.8 mg of liraglutide or a placebo once daily and observed for 3.5 years. Results showed a 13% reduction in major adverse cardiovascular events (MACEs), a 15% lower overall mortality, and a 22% reduction in cardiovascular-related deaths among those receiving liraglutide treatment compared to the placebo group. However, no significant differences were noted between the groups in nonfatal myocardial infarctions or nonfatal strokes<sup>[41]</sup>.

<sup>11</sup> Semaglutide has been the focus of two extensive cardiovascular outcome trials: The Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes 6 (SUSTAIN-6) trial and the Oral Semaglutide and Cardiovascular Outcomes in Patients with T2DM (PIONEER 6 trial). In the SUSTAIN-6 trial, 3297 individuals with T2DM and elevated cardiovascular risk, 83% with established cardiovascular disease were randomly assigned to receive subcutaneous injections of once-weekly semaglutide at doses of 0.5 mg or 1 mg, or a placebo. Over a median period of 2.1 years, the trial revealed a significant 26% reduction in MACE in semaglutide-treated subjects, primarily driven by a substantial decrease in nonfatal stroke events. It is noteworthy to mention that semaglutide-treated individuals reported a higher incidence of complications associated with retinopathy<sup>[42]</sup>.

On the other hand, in the PIONEER 6 trial, which assessed oral semaglutide, the administration of a once-daily 14 mg dose did not result in a reduced rate of MACE, nonfatal myocardial infarctions, or nonfatal strokes. However, a significant reduction in

cardiovascular deaths was evident among participants who received oral semaglutide<sup>[30]</sup>.

In the Effect of Efglenatide on Cardiovascular Outcomes (AMPLITUDE-O) trial, which included 4076 patients with T2DM and either prior cardiovascular disease or existing kidney disease along with at least one additional cardiovascular risk factor, the occurrence of MACE was significantly reduced by 27% in those who received efpeglenatide compared to a placebo. Furthermore, the efpeglenatide group exhibited a notably reduced risk of hospitalization for heart failure<sup>[43]</sup>.

The HARMONY outcomes trial involved 9463 individuals <sup>2</sup> with T2DM and established cardiovascular disease who were randomly assigned to receive either a 30 mg weekly dose of albiglutide or a placebo. After a median follow-up period of 1.5 years, the albiglutide group exhibited a 22% reduced risk of MACE. However, there was no statistically significant difference in the risk of cardiovascular, all-cause mortality, and stroke<sup>[44]</sup>.

In the SURPASS-4 trial, 2002 participants were randomly assigned to receive either tirzepatide at varying strengths (5 mg, 10 mg, or 15 mg) or insulin glargine. The study observed participants experiencing adjudicated MACE events, including cardiovascular death, myocardial infarction, stroke, and hospitalization for unstable angina. Importantly, the occurrence of these events was not higher in the tirzepatide group when compared to the glargine group and it was concluded that tirzepatide treatment was not associated with increased cardiovascular risk<sup>[45]</sup>.

Additionally, the ongoing SUMMIT <sup>8</sup> trial aims to evaluate tirzepatide's effects on individuals with both obesity and heart failure with preserved ejection fraction. Participants will receive tirzepatide or a placebo for 52 wk, with the primary outcome being a composite endpoint that includes mortality, heart failure events, exercise capacity, and heart failure symptoms<sup>[46]</sup>. In summary, the outcomes of the previously mentioned trials provided strong support for the utilization of dual GIP and GLP-1 RAs in individuals with T2DM and established or significant risk of cardiovascular disease.



### *The nephroprotection effect of dual GIP and GLP-1 RAs*

GLP-1 RAs exhibit nephroprotective effects independently of their impact on blood glucose levels. In addition to inducing natriuresis and diuresis, GLP-1 RAs demonstrate antioxidative and anti-inflammatory properties. One of these involves the activation of the cyclic adenosine monophosphate-protein kinase A pathway, reducing the nicotinamide adenine dinucleotide phosphate oxidative activity and the reactive oxygen species production in the diabetic kidney<sup>[17]</sup>.

Furthermore, GLP-1 RAs promote the reduction of mesangial expansion and the elevation of nitric oxide levels within the glomeruli, ultimately improving glomerular filtration and hemodynamic function, all of which help inhibit the progression of diabetic kidney disease. Moreover, GLP-1 RAs have been shown to decrease markers of renal renin-angiotensin-aldosterone system (RAAS) activation, including angiotensin II levels, and mitigate its detrimental effects within the glomerulus. However, comprehensive data regarding the effects of acute or long-term GLP-1 RA treatment on circulating RAAS components are still lacking. Natriuresis, lowering plasma renin activity, renal oxidative stress, improving blood pressure, and glycemic control collectively contribute to the anti-albuminuric effects observed with GLP-1 RAs<sup>[17]</sup>.

In the LEADER trial, liraglutide reduced the incidence of new or worsening nephropathy by 22% and showed a slight deceleration in the decline of the estimated glomerular filtration rate (eGFR) over time when compared to a placebo. In the SUSTAIN-6 trial, semaglutide reduced the risk of persistent macroalbuminuria. However, both trials revealed no significant differences in more severe renal outcomes, such as doubling of serum creatinine levels or the need for renal replacement therapy<sup>[41,42]</sup>. In the SURPASS-4 trial, tirzepatide significantly slowed the rate of eGFR decline, reduced the urinary albumin-to-creatinine ratio, and reduced the incidence of the composite kidney endpoint (time to first occurrence of eGFR decline of at least 40% from baseline, ESRD, kidney failure related death, or new-onset macroalbuminuria) in patients with T2DM compared to insulin glargine<sup>[45]</sup>.

### ***Contraindications and precautions for GLP-1 and dual GIP and GLP-1 RAs use***

**Pancreatitis risk:** Although the exact mechanism remains largely unidentified, cases of acute pancreatitis, including potentially fatal hemorrhagic and necrotizing forms, have been documented among users of GLP-1 RAs. Meanwhile, it is unclear whether a direct cause-and-effect relationship exists between GLP-1 RAs and pancreatitis or pancreatic cancer. Since the data remains unclear, patients with a history of pancreatitis should not be treated with GLP-1 Ras<sup>[47]</sup>.

**T1DM:** Certain beneficial effects of GLP-1 RAs, such as reducing glucagon levels and promoting weight loss, are not reliant on the functioning of islet cells. This could potentially be advantageous for certain individuals with T1DM. However, as of now, until more data becomes available, studies refrain from prescribing GLP-1 RAs for patients with T1DM<sup>[48]</sup>.

**Renal impairment:** <sup>22</sup> In patients with severe renal impairment (eGFR 15 to 29 mL/min) and end-stage renal disease, lixisenatide and albiglutide are not recommended as there is limited experience with these drugs in this population<sup>[49,50]</sup>. However, a study showed that a 5 mg dose of tirzepatide was tolerated in patients with renal impairment, and no effect on the pharmacokinetics was observed<sup>[51]</sup>.

**Gastroparesis & inflammatory bowel disease:** Patients with gastroparesis and inflammatory bowel disease should avoid GLP-1 analogs. The mechanisms by which GLP-1 and incretin-based therapies affect gut motility are not fully understood but research conducted on the duodenum and colon of rodents suggests <sup>17</sup> that GLP-1 can reduce excitatory cholinergic neurotransmission in the enteric nervous system by acting on presynaptic GLP-1 receptors, which in turn modulate the release of nitric oxide<sup>[52]</sup>. Therefore, GLP-1 RAs could potentially be employed as a treatment to relieve symptoms in individuals with irritable bowel syndrome *via* decreasing motility in the



intro-duodenal-jejunal region and inhibiting the migrating motor complex in both healthy individuals and patients<sup>[53]</sup>.

**Thyroid cancer:** Concerns exist regarding a potential link between GLP-1 RAs and thyroid cancer, supported by rodent studies showing associations with thyroid C-cell proliferation and neoplasia. Conflicting evidence and controversies have arisen from clinical trials and databases regarding this matter in human studies. In humans, the GLP-1 receptor was identified in 18% of papillary thyroid carcinomas and 33% of control thyroid lobes, including neoplastic and hyperplastic lesions of thyroid C-cells<sup>[34,36,54-56]</sup>. Additionally, GLP-1 may function through the phosphoinositol-3 kinase/AKT serine/threonine kinase pathway and/or mitogen-activated protein kinase/extracellular signal-regulated kinase pathway, which play a crucial role in controlling cell growth and proliferation and are closely associated with cancer, including papillary thyroid carcinoma<sup>[57]</sup>. Additionally, a recent study identified an elevated risk of all types of thyroid cancers and medullary thyroid cancer associated with the use of GLP-1 RA, particularly notable after 1-3 years of treatment duration<sup>[58]</sup>. However, a recent meta-analysis study revealed a significant 28% increase in the overall risk of thyroid disorders when using GLP-1 RAs compared to placebos or other interventions but no significant correlation with thyroid cancer was identified<sup>[59]</sup>. Although evidence in human studies remains inconclusive, GLP-1 RAs are contraindicated in patients with personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2<sup>[34,59]</sup>.

**Hypersensitivity and other contraindications:** While hypersensitivity reactions to GLP-1 RAs are rare, in cases where an individual has a history of such a reaction to any GLP-1 RA, it is typically advisable to opt for an alternative glucose-lowering agent that does not belong to the GLP-1 RA class. Furthermore, other relative contraindications may exist, such as acute gallbladder diseases like acute cholecystitis with GLP-1 RA in general or diabetic retinopathy specifically with semaglutide use<sup>[60,61]</sup>.

### *The cost burden of dual GIP and GLP-1 RAs*

Cost considerations play a crucial role in the selection of medication and switching between them. A cost-effectiveness analysis in Saudi Arabia found that semaglutide was the most financially advantageous option, with the lowest cost of achieving glycemic control to reach target HbA1C levels compared to other GLP-1 RAs (liraglutide, dulaglutide, exenatide, and lixisenatide)<sup>[62]</sup>. A study in Taiwan found that GLP-1 RA therapy had higher costs per patient compared to insulin from the payer perspective, but that the GLP-1 RA group incurred lower costs than the insulin group in the healthcare sector, primarily due to decreased expenses related to emergency visits and in-patient admissions. Despite increased drug costs, real-world GLP-1 RA usage showed cost-effectiveness, with lower healthcare costs linked to lower mortality and hypoglycemia-related hospitalizations<sup>[63]</sup>. In a United States database study, once-weekly dulaglutide had similar diabetes-related total costs to daily liraglutide but was associated with higher costs compared to once-weekly exenatide<sup>[64]</sup>.

### **SWITCHING BETWEEN DIFFERENT GLP-1 AND DUAL GLP-1/GIP RAS**

There is a lack of consensus on how to switch between different GLP-1 and dual GLP-1/GIP RA agonists, and no evidence or guidelines to follow for switching, so we relied on clinical practice experiences from members in this research group in different settings both inside and outside Saudi Arabia. However, further study in this regard is warranted. Switching between GLP-1 and dual GLP-1/GIP RAs may be required for several reasons including drug availability, adherence, patient preference, cost, drug tolerability, side effects, and efficacy. When switching from one agent to another, it is crucial to first address the reason for switching, and then, based on the duration and dose of the previous GLP-1 RA or dual GLP-1/GIP RA, along with the patient's experience, especially the GI side effects, an individualized approach is recommended<sup>[64]</sup>.

For those with GI side effects, we consider stepwise medication withdrawal to determine the causative agent and facilitate medication tolerance before switching. We ensure that all recommended measures to mitigate GI side effects have been taken, such as ensuring that the patient is receiving the recommended dosage of the GLP-1 or dual GLP-1/GIP RA as dose reduction can frequently reduce or eliminate GI side effects; ensuring that dietary recommendations are followed (eating smaller portions and avoiding high-fat meals); and trying other mitigating measures such as implementing a short-term liquid diet or using natural antinausea remedies like ginger or peppermint<sup>[64]</sup>.

For patients who cannot tolerate GLP-1 or dual GLP-1/GIP RAs despite the mitigating measures, we recommend waiting until symptoms subside, then initiating the new GLP-1 or dual GLP-1/GIP RA therapy at the lowest dose, and then considering a slower dose up-titration<sup>[65]</sup>. For patients who can tolerate GLP-1 or dual GLP-1/GIP RAs but are changing their medication for other reasons, starting the new medication at an equivalent dose is a reasonable approach. It helps to ensure a smooth transition while maintaining the desired therapeutic effect. These equivalent doses are suggested based on results from several studies and are illustrated in Table 3<sup>[33,64,66]</sup>.

When switching from a drug administered once or twice daily such as liraglutide, oral semaglutide, or exenatide, we advise initiating the new product the day after discontinuing the original product. On the other hand, when switching from a drug administered weekly such as dulaglutide, semaglutide, exenatide extended release, or tirzepatide, we suggest beginning the new drug seven days after discontinuing the original drug.

<sup>1</sup> For patients who are tolerating the maximum therapeutic dose of a once-daily or twice-daily GLP-1 RA (exenatide 10 µg twice daily, liraglutide 1.8 mg once daily, or lixisenatide 20 mg once daily), but are switching to a once-weekly GLP-1 RA, we recommend starting dulaglutide or exenatide once-weekly at the maximum therapeutic dose (dulaglutide 1.5 mg, exenatide 2 mg) to decrease the HbA1C. For subcutaneous semaglutide and tirzepatide, we recommend starting at the intermediate once-weekly

dose (semaglutide 0.5 mg and tirzepatide 5 mg) for 4 wk before transitioning to the maximum therapeutic dose. This approach can help minimize adverse GI events. However, when switching from 1 mg semaglutide to tirzepatide, it is better to start tirzepatide with the 5 mg dose, as the HbA1C lowering effects of 5 mg tirzepatide and 1 mg semaglutide are similar. Later, the dose of tirzepatide can be increased to 7.5 mg and 10 mg after four weeks<sup>[31]</sup>. For patients receiving subcutaneous once-weekly injections to be switched to once-daily oral semaglutide, manufacturers suggest initiating a 7 mg or 14 mg dose seven days after their last injection. In contrast, patients receiving oral semaglutide 14 mg once daily can be switched to subcutaneous injection of semaglutide 0.5 mg, tirzepatide 5 mg, or dulaglutide 1.5 mg once-weekly the day after their last oral dose<sup>[25,67]</sup>.

## **OTHER CONSIDERATIONS**

### ***Concerns over gastric stasis with GLP-1 and dual GLP-1/GIP RAs***

The inhibitory effect on gastric motility and delayed gastric emptying seems to be a crucial factor contributing to the ability of GLP-1 RAs to reduce postprandial glycemia. GLP-1 RAs have demonstrated a dose-dependent deceleration of gastric emptying in both healthy and diabetic individuals; this effect applies to both the solid and liquid components of a meal<sup>[53]</sup>. This phenomenon is believed to be due to the rapid tachyphylaxis at the level of the vagal nerve activation<sup>[68,69]</sup>. However, the inhibitory effect of GLP-1RAs on gastric emptying might be diminished or absent in patients with diabetic-related dysautonomia<sup>[70]</sup>.

Contrary to the prevailing expectation that long-acting GLP-1 RAs would lose their ability to slow gastric emptying with prolonged use, a study involving liraglutide revealed a persistent deceleration of gastric emptying, as assessed through scintigraphy, even after 16 wk of treatment. While the degree of deceleration was less pronounced than at the 5-wk mark, it remained significant<sup>[71]</sup>. Accordingly, it is now evident that both short- and long-acting GLP-1 RAs can continue to cause slow gastric emptying

when used consistently, although short-acting GLP-1 RAs exhibit a more pronounced effect<sup>[53,68-72]</sup>.

The reduction in postprandial glucose levels is closely associated with the extent of gastric emptying deceleration, as well as the baseline emptying rate. Importantly, baseline gastric emptying rates vary considerably among individuals, but this variability is less pronounced over time within individuals<sup>[25,53,64-68]</sup>. Hence, GLP-1 RA therapy could be considered for individuals with faster gastric emptying, which is often observed in cases of obesity and uncomplicated T2DM<sup>[71-74]</sup>.

### ***Preoperative management of patients on GLP-1 or dual GLP-1/GIP RAs***

As discussed previously, GLP-1 RAs have been associated with several side effects such as nausea and vomiting which can be traced to their core mechanism of delaying gastric emptying. Recent findings from a case report and a retrospective study have shed light on significant clinical concerns<sup>[75,76]</sup>. They showed that patients exhibited residual gastric content even during the fasting period, which significantly increased the risk of pulmonary aspiration, with a causative factor attributed to the GLP-1 Ras<sup>[75,76]</sup>. Considering this evidence, The American Society of Anesthesiologists as part of preoperative management, recommends withholding all types of GLP-1 RAs before any elective surgery for one day before surgery on daily doses and one week on weekly doses. Similarly, this can be extrapolated to dual GLP-1/GIP RA agents as well.

### ***Missed doses***

For the once-daily liraglutide, oral semaglutide, or twice-daily exenatide, patients may skip the missed dose and resume treatment with the next scheduled dose<sup>[22,23,25]</sup>. However, if a dose of lixisenatide is missed, the missed dose should be administered 1 h prior to the next meal<sup>[24]</sup>. For the once-weekly exenatide or dulaglutide, the missed dose should be administered as soon as possible if there are  $\geq 72$  h until the next scheduled dose. If there are  $< 72$  h before the next scheduled dose, the missed dose can be skipped and the next scheduled dose can be administered on time<sup>[20-22]</sup>.



Regarding the injectable once-weekly semaglutide, administration is allowed within five days after the missed dose. However, if more than five days have passed, the dose can be skipped, and the next scheduled dose can be administered on time<sup>[25]</sup>. For tirzepatide, administration is done within four days after the missed dose. However, if more than four days have passed, the dose can be skipped, and the next scheduled dose administered on time<sup>[26]</sup>.

### ***Pregnancy and lactation***

Generally, GLP-1 RAs are considered a category C drug in pregnancy due to reports of it being teratogenic in rat and rabbit controls; thus, their usage in pregnant women should be weighed against the risks of fetal complications<sup>[36]</sup>. Nevertheless, despite the paucity of research on their applicability and safety in humans during pregnancy, case reports have reported an uneventful pregnancy with the accidental usage of GLP-1 RAs during the first trimester of pregnancy<sup>[77,78]</sup>. However, the United States FDA advocates against the use of all GLP-1 and dual GLP-1/GIP RAs, including tirzepatide, for pregnant individuals and recommends the usage of contraception during the treatment period<sup>[23,25,26,74]</sup>. Additionally, it is recommended to wait for at least two months before planning pregnancy as a wash-out period in patients using injectable semaglutide<sup>[25]</sup>. It is important to note that the effectiveness of oral hormonal contraception may decline while a patient is on tirzepatide therapy<sup>[55,56]</sup>. Lastly, experience with the use of GLP-1 RAs in breastfeeding women is limited; therefore, their use is not recommended during lactation<sup>[55]</sup>.

### ***Use of GLP-1 or dual GLP-1/GIP RAs after bariatric surgery***

Postprandial hyper-insulinemic hypoglycemia, a challenging metabolic phenomenon following bariatric surgery, continues to be a conflicting and stubborn complication to address. Continuous blood glucose monitoring indicates that it may happen in approximately 55% of individuals following laparoscopic vertical sleeve gastrectomy and up to 75% after roux Y gastric bypass. Moreover, a significant number of these



instances of hypoglycemia occur without any other accompanying symptoms. A recent systematic review indicated that GLP-1 RAs may potentially decrease the frequency of postprandial hypoglycemic episodes and enhance glycemic stability<sup>[79]</sup>. However, another study examining meal effect in humans after gastric bypass surgery showed that the augmented secretion and activity of GLP-1 play a significant role in post-meal hyperinsulinemia and altered glucose metabolism. This effect is particularly pronounced in individuals who experience hyperinsulinemia after gastric bypass surgery<sup>[80]</sup>. In addition, GLP-1 RAs showed a potential role in the remission of psoriasis, as noted in case reports following bariatric surgery, which opens up intriguing avenues for research and potential novel approaches to treating psoriasis<sup>[81]</sup>.

In a recent review, semaglutide was deemed a viable treatment option for individuals experiencing weight regain following bariatric surgery<sup>[82]</sup>. On the other hand, no specific studies have been conducted to evaluate tirzepatide in post-bariatric surgery patients<sup>[83]</sup>. The initial data on the effectiveness of semaglutide in this patient group has recently emerged from a retrospective observational study conducted in Germany. This study involved patients who had either achieved inadequate weight loss or experienced weight regain after bariatric surgery. Following six months of weekly subcutaneous administration of semaglutide at a maximum dosage of 0.5 mg, an average reduction in total body weight of 10.3% was observed<sup>[84]</sup>.

In another retrospective observational study involving 50 patients who experienced weight regain after bariatric surgery, the effectiveness of GLP-1 RAs liraglutide and semaglutide in reducing weight was investigated. The study found that after 6 mo of GLP-1 RA therapy, the median percentage of total body weight loss was 8.8%. Additionally, more than 75% of patients lost over 5% of their initial weight, and over 33% of them lost more than 10%. On average, patients had shed 67.4% of the weight they had regained after their last bariatric procedure. Adverse events were recorded in roughly one-third of the patients, but they were all mild, temporary, and primarily related to the GI system. Overall, these findings endorse the safe use of both GLP-1 RAs

for achieving clinically significant weight loss, amounting to roughly two-thirds of the weight gained after bariatric surgery<sup>[85]</sup>.

#### *Use of GLP-1 or dual GLP-1/GIP RAs in patients with renal insufficiency*

Recently, there have been some post-marketing reports of acute renal injury or deterioration of pre-existing chronic kidney failure in patients treated with GLP-1 RAs. In certain cases, these conditions have necessitated the use of hemodialysis. It is worth noting that some of these events have been observed in patients without previously diagnosed kidney issues. <sup>23</sup> The majority of the documented cases occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration during GLP-1 RAs treatment. Therefore, it is important to monitor the kidney functions in patients who are on GLP-1 RAs and complain of severe GI reactions<sup>[20-26]</sup>.

It is not advisable to use GLP-1 RAs in patients with severe kidney dysfunction (creatinine clearance < 30 mL/min) or end-stage renal disease. Also, extreme caution is advised when prescribing GLP-1 RAs to patients with kidney transplantation or moderate kidney dysfunction (creatinine clearance 30-50 mL/min)<sup>[20-26]</sup>.

The latest clinical trials have provided significant evidence of GLP-1 RAs demonstrating improvements in kidney function. One noteworthy trial is the LIRA-RENAL trial, which focused on evaluating the effectiveness and safety of liraglutide in <sup>2</sup> diabetic patients with moderate kidney dysfunction (defined as eGFR 30-59 mL/min). This trial showed that adding liraglutide to the already existing glucose-lowering therapy significantly reduced HbA1C levels compared to the placebo treatment (-1.05% vs -0.38%). Notably, the trial revealed no worsening in kidney function among the participants, and patients treated with liraglutide as compared to those who received the placebo showed a lower increase in albuminuria<sup>[86]</sup>.

Another notable trial is the <sup>2</sup> AWARD-7 trial which compared the benefits of the long-acting GLP-1 analog dulaglutide and insulin glargine on kidney functions in patients with T2DM and moderate-to-severe chronic kidney disease. The trial involved 577 participants who <sup>24</sup> were randomly assigned to three groups: Dulaglutide 1.5 mg,

dulaglutide 0.75 mg, and insulin glargine. After 52 wk of treatment, the decline in the eGFR was significantly less in the dulaglutide-treated groups compared to the insulin group. This study confirmed the independent advantage of dulaglutide over glargine on the eGFR. Also, in the SUSTAIN-6 trial, patients receiving semaglutide had a lower rate of persistent macroalbuminuria compared to the placebo group<sup>[87]</sup>. The pharmacokinetic outcomes and renal benefits of clinical trials with GLP-1 and dual GLP-1/GIP RA agents are shown in Table 4<sup>[88]</sup>.

Many pathophysiological mechanisms are attributed to the nephroprotective effect of GLP-1 RAs, one of which is the definite robust glycemic control achieved by the addition of GLP-1 RAs to the antidiabetic regimen of the patient which prevents the effect of high glucose concentration on increased filtration rate of proteins *via* the glomerular capillary membrane and on impaired tubular reabsorption<sup>[42]</sup>. Another possible theory is that it suppresses inflammation-related pathways thus resulting in anti-inflammatory and antioxidative effects<sup>[89]</sup>.

#### *Use of GLP-1 or dual GLP-1/GIP RA during fasting*

Fasting, as in the holy month of Ramadan, traditionally takes place from dawn to sunset. During this time, patients with diabetes mellitus may face some challenges in their daily doses and timing of medications. Different trials have demonstrated that the use of GLP-1 RAs during Ramadan is safe and effective with better glycemic control and weight reduction<sup>[90-94]</sup>. GLP-1 RAs have a potential hypoglycemia risk when used with other glucose-lowering agents<sup>[95]</sup>. Weekly injectable agents can be considered a good choice for fasting patients. It would be advisable to commence the weekly doses 4-8 wk before the month of Ramadan to closely monitor potential dehydration or GI upset to allow titration for tolerance<sup>[91]</sup>. Additional studies are required to determine the safety and effectiveness of tirzepatide and oral semaglutide during Ramadan. Based on previous data, liraglutide and lixisenatide were found to be safe, therefore, GLP-1 RAs are unlikely to cause hypoglycemia during prolonged fasting. For example, exenatide was associated with a non-significant percentage of hypoglycemic events (0.08%),

liraglutide was associated with fewer symptomatic hypoglycemia compared with sulfonylurea ( $P = 0.0009$ ), lixisenatide and basal insulin led to fewer events compared to sulfonylurea and basal insulin (odds ratio = 0.22; 95% confidence interval: 0.07-0.7)<sup>[90-92]</sup>.

## **CONCLUSION**

The utilization and switching between GLP-1 and dual GLP-1/GIP RAs pose complex challenges in various clinical scenarios; challenges that have gained prominence with the increased availability of newer agents within these drug classes. While numerous studies have undertaken comparative evaluations among GLP-1 or dual GLP-1/GIP RAs, more studies are needed to examine the implications of switching between these emerging agents. This deficiency exposes a critical research gap, especially for healthcare professionals who are contemplating such transitions. Our aim is to accumulate clinical insights and offer practical guidance to healthcare practitioners navigating utilization and switching between GLP-1 or dual GLP-1/GIP RAs. This endeavor necessitates a comprehensive consideration of patient preferences, clinical variables, potential associated risks, and anticipated benefits.

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