World Journal of Diabetes

Submit a Manuscript: https://www.f6publishing.com

World J Diabetes 2024 March 15; 15(3): 331-347

DOI: 10.4239/wjd.v15.i3.331

ISSN 1948-9358 (online)

REVIEW

Practical guide: Glucagon-like peptide-1 and dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonists in diabetes mellitus

Saleh Fahad Alqifari, Omar Alkomi, Abdullah Esmail, Khadijeh Alkhawami, Shahd Yousri, Mohamad Ayham Muqresh, Nawwarah Alharbi, Abdullah A Khojah, Ahmed Aljabri, Abdulrahman Allahham, Kousalya Prabahar, Hanan Alshareef, Mohammed Aldhaeefi, Tariq Alrasheed, Ali Alrabiah, Laila A AlBishi

Specialty type: Endocrinology and metabolism

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Horowitz M, Australia; Long P, China; Tang ZP, China

Received: October 1, 2023
Peer-review started: October 1, 2023
First decision: November 21, 2023
Revised: December 6, 2023
Accepted: January 15, 2024
Article in press: January 15, 2024
Published online: March 15, 2024

Saleh Fahad Alqifari, Kousalya Prabahar, Hanan Alshareef, Department of Pharmacy Practice, Faculty of Pharmacy, University of Tabuk, Tabuk 71491, Saudi Arabia

Omar Alkomi, Abdullah Esmail, Khadijeh Alkhawami, Shahd Yousri, Mohamad Ayham Muqresh, Nawwarah Alharbi, Abdulrahman Allahham, Department of Clinical Sciences, Sulaiman Alrajhi University - College of Medicine, Al Bukayriyah 52726, Saudi Arabia

Abdullah A Khojah, Department of Family Medicine, Dr. Soliman Fakeeh Hospital DSFH, Jeddah 21461, Saudi Arabia

Ahmed Aljabri, Department of Pharmacy Practice, Faculty of Pharmacy, King Abdulaziz University, Jeddah 22252, Saudi Arabia

Mohammed Aldhaeefi, Clinical and Administrative Pharmacy Sciences, College of Pharmacy, Howard University, Washington, DC 20059, United States

Tariq Alrasheed, Department of Internal Medicine, Faculty of Medicine, University of Tabuk, Tabuk 71491, Saudi Arabia

Ali Alrabiah, Department of Pharmacy Practice, Raabe College of Pharmacy, Ohio Northern University, Ohio, OH 45810, United States

Laila A AlBishi, Department of Pediatric, Faculty of Medicine, University of Tabuk, Tabuk 71491, Saudi Arabia

Corresponding author: Saleh Fahad Alqifari, PharmD, Assistant Professor, Chief Pharmacist, Department of Pharmacy Practice, Faculty of Pharmacy, University of Tabuk, King Faisal Road, Tabuk 71491, Saudi Arabia. salqifari@ut.edu.sa

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 insulinotropic polypeptide (GIP)/GLP-1 RA, 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 insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist; Clinical practice; Endocrinology

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 insulinotropic polypeptide (GIP) and GLP-1 RAs have now emerged as the newest addition to the long-acting injectables. 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 RA and dual GIP and GLP-1 RA use in everyday clinical practice.

Citation: Alqifari SF, Alkomi O, Esmail A, Alkhawami K, Yousri S, Muqresh MA, Alharbi N, Khojah AA, Aljabri A, Allahham A, Prabahar K, Alshareef H, Aldhaeefi M, Alrasheed T, Alrabiah A, AlBishi LA. Practical guide: Glucagon-like peptide-1 and dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonists in diabetes mellitus. *World J Diabetes* 2024; 15(3): 331-347
URL: https://www.wjgnet.com/1948-9358/full/v15/i3/331.htm
DOI: https://dx.doi.org/10.4239/wjd.v15.i3.331

INTRODUCTION

The glucose-dependent insulinotropic 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[1]. 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[2,3]. Additionally, these agents delay gastric emptying, a factor that significantly influences the pace of alcohol absorption, and a determinant of plasma ethanol response. When gastric emptying is slower, absorption is delayed, leading to lower peak blood alcohol concentration[4,5].

Therefore, research focused on developing drugs that simulated the action of these hormones. In 2005, exenatide became the first approved GLP-1 receptor agonist (GLP-1 RA) for the treatment of type 2 diabetes mellitus (T2DM)[6]. Later, more GLP-1 RAs were approved, and they showed good results in improving glycemic control and reducing weight[7,8]. 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[9]. 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[10]. 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[11-13]. Currently, it is important to highlight that long-acting GLP-1 RA have been predominantly replaced short-acting GLP-1 RA, despite the fact that exenatide BID is now considered off-patent.

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[14-17]. 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[17]. Likewise, for patients with an initial HbA1C level < 7.5% as well, GLP-1 RAs are recommended as a second-line agent[17]. On the other hand, for patients with an entry HbA1C level of 7.5%, a strategy of dual therapy including GLP-1 RAs as a first-line therapy in addition to metformin is recommended [16]. 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[14-16]. Furthermore, GLP-1 RAs are indicated as a first-line intervention when metformin is contraindicated[14-16]. 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[14-19].

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 paper 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 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 the 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.

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[20-27]. 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[20-27]. 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[28]. Consequently, structural modifications were made by removing amino acids or adding fatty acid chains to confer resistance to enzymatic degradation[28].

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[29]. This novel compound has been found to significantly improve glycemic control and manage inadequate response in patients receiving insulin glargine [30].

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[21-27].

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[31].

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 [32]. Tirzepatide has an approximate bioavailability of 80%, and the time that 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 L. 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[32,33]. 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 4 wk[32].

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[33]. 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[33]. 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[33].

Regarding the tirzepatide age threshold, its distribution in the SURPASS 1-5 studies 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 who may exhibit heightened sensitivity to the treatment cannot be definitively ruled out[27]. 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[34].

Table 1 Characteristics of glucagon-like peptide-1 receptor agonists

Name	MOA	ROA	Available doses	Frequency	HbA1C reduction	Elimination and dose adjustment	Half-life	Dosing instructions	Drug-interactions
Lixisenatide	GLP-1 receptor agonist	SC	Initial: 14 doses of 10 μg per dose Followed by: 14 doses of 20 μg per dose	Once daily	-0.65 (after 12 wk of monotherapy) compared with placebo, -0.46 (in 24 wk), -0.27 in combination with metformin +/- sulfonylurea (in 24 wk), -0.48 in combination with pioglitazone +/- metformin (in 24 wk), -0.28 in combination with insulin glargine and metformin +/- thiazolidinediones (in 24 wk)	Renal elimination, dependent on GFR Insufficient data on ESRD. No dose adjustment for mild or moderate renal impairment	Approximately 3 h	1 h before meals Oral medications 1 h before injection	Delayed gastric emptying, decreased absorption and decreased effectiveness of some oral medications
Exenatide	GLP-1 receptor agonist	SC	Initial: 60 doses of 5 μg per dose Followed by: 60 doses of 10 μg per dose	BID	After 30 wk: -0.5 for 5 μg once daily, -0.7 for 10 μg once daily, -0.5 for 5 μg BID, -0.9 for 5 μg BID -0.8 and -1.0 for 5 and 10 μg, respectively, in combination with metformin and sulfonylurea	Renal elimination Avoided in ESRD and severe renal impairment. No dose adjustment for mild renal impairment	2.4 h	1 h before the two main meals The meals must be 6 h apart	Increased INR in patients with warfarin
Exenatide extended release	GLP-1 receptor agonist	SC	2 mg	Every 7 d	No significant difference from metformin and pioglitazone after 26 wk, -0.39 as compared to sitagliptin use -0.63 in combination with metformin as compared to sitagliptin, and -0.32 when compared to pioglitazone (in 26 wk), -0.64 in combination with glargine (in 28 wk)	Renal elimination Avoided in ESRD and severe renal impairment	2-4 wk	At any time of the day	Increased INR in patients with warfarin May impact the absorption of oral medications
Liraglutide	GLP-1 receptor agonist	SC	Initial: 0.6 mg for 1 wk Followed by: Increase to 1.2 mg If additional glycemic control needed increase to 1.8 mg after 1 wk	Once daily	-0.3 and -0.6 for 1.2 and 1.8 mg, respectively, after 52 wk compared to glimepiride. Both doses showed -1.1 when combined with metformin compared to placebo in 26-wk trial. -0.3 and -0.6 for 1.2 and 1.8 mg, respectively, in 26-wk trial when combined with metformin compared with sitagliptin; -1.06 in combination with metformin and basal insulin compared to placebo	No specific organ as main part of elimination No dose adjustment is needed for renal disease Should be used cautiously in patients with hepatic impairment as sufficient data is absent for this population	13 h	At any time of the day	Delayed gastric emptying
Dulaglutide	GLP-1 receptor agonist	SC	0.75 mg 1.5 mg if additional	Every 7 d	-0.5 and -0.7 for 0.75 and 1.5 mg, respectively, when compared to	No specific organ as main part of elimination	5 d	At any time of the day	Potential decrease in absorption of oral

			glycemic control is needed Increase the dose by 1.5 mg, at least 4 wk after the previous dose, maximum dose 4.5 mg		sitagliptin in 52-wk trial; -1.1 for 1.5 mg combined with glimepiride when compared to placebo; -0.7 for 1.5 mg combined with basal insulin in 26-wk trial				medications
Tirzepatide	Glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist	SC	Initial: 2.5 mg	Every 7 d	-1.7, -1.6, and -1.6 for 5, 10, and 15 mg, respectively, when compared to placebo in 40-wk trial; -0.2, -0.4, and -0.5 for 5, 10, and 15 mg, respectively, when compared to semaglutide in 40-wk trial; -0.6, -0.8, and -0.9 for 5, 10, and 15 mg, respectively, when compared to insulin degludec in 52 wk	Hepatic and renal elimination	5 d	At any time of the day	Potential decrease in absorption of oral medications
			After 4 wk increase the dose to 5 mg		-0.7, -0.9, and -1 for 5, 10, and 15 mg, respectively, when compared to insulin glargine in 52 wk	No dose adjustment is needed for renal and hepatic diseases			
			Increase the dose at 2.5 mg, at least 4 wk apart from the previous dose, maximum dose 15 mg						
Semaglutide	GLP-1 receptor agonist	SC	Initial dose 0.25 mg After 4 wk increase the dose to 0.5 mg If additional glycemic control needed increase to 1 mg after 4 wk, and if further control is required increase to 2 mg after 4 wk of 1 mg dose	Every 7 d	-1.4 and -1.6 for 0.5, and 1 mg, respectively, when compared to placebo in 30 wk trial; -0.6 and -0.8 for 0.5 and 1 mg, respectively, when compared to placebo in 56-wk trial; -0.5 for 1 mg in comparison with exenatide in combination with metformin or metformin with sulfonylurea	Hepatic and renal elimination No dose adjustment is needed for renal and hepatic diseases	1 wk	At any time of the day	Potential decrease in absorption of oral medications
Oral Semaglutide	GLP-1 receptor agonist	Oral	Initial dose: 3 mg for 30 d Followed by: 7 mg	Once daily	-0.9 and -1.1 for 7 and 14 mg, respectively, when compared to placebo in 26 wk trial	Hepatic and renal elimination No dose adjustment needed for renal and hepatic diseases	1 wk	30 min before any oral intake	Potential decrease in absorption of oral medications

	If additional glycemic control needed increased to 14 mg after 30 d of 7 mg dose	-0.3 and -0.5 for 7 and 14 mg, respectively, when compared to sitagliptin in 26-wk trial; -0.1 for 14 mg dose when compared with liraglutide; 0.9 and -1.2 for 7 and 14 mg, respectively, combined with insulin when compared to placebo in 26-wk trial

MOA: Mechanism of action; ROA: Route of administration; HbA1C: Glycated hemoglobin; GFR: Glomerulus filtration rate; ESRD: End-stage renal disease; BID: Twice daily; GLP-1: Glucagon-like peptide-1; INR: International normalized ration; SC: Subcutaneous injection.

Comparison of tirzepatide with semaglutide: In a recent trial, tirzepatide, administered at a dose 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 [32]. 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[32]. 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[32,35].

In the same study, among patients with T2DM, it was found that tirzepatide achieved a superior reduction in HbA1C levels compared to semaglutide[32]. In patients who were administered tirzepatide, the risk of hypoglycemia (defined as a blood glucose level below 54 mg/dL) was reported as 0.6% 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[32]. 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, 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[32,35]. 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 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[32,35].

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[35,36]. 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[35,36]. Furthermore, to avoid any delay in drug absorption, it is recommended to take interacting drugs approximately 1 h before administering GLP-1 Ras[35].

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[37,38]. 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[39].

GLP-1 RAs display anti-inflammatory properties by reducing the production of proinflammatory cytokines such as tumor necrosis factor-α, interleukin (IL)-6, and IL-1β and the C-reactive protein levels[40,41]. 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 inflam-

matory cells, particularly monocytes and neutrophils, through the vascular wall, which reduces the formation of atherosclerotic plaque[42]. Moreover, GLP-1 RAs demonstrated anti-aggregation effects on the activity of murine and human platelets in numerous preclinical studies[43].

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.

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 [44].

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 a dose 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 MACEs 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[45].

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 MACEs, nonfatal myocardial infarctions, or nonfatal strokes. However, a significant reduction in cardiovascular deaths was evident among participants who received oral semaglutide[31].

In the Effect of Efpeglenatide 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 MACEs 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[46].

The HARMONY Outcomes trial involved 9463 individuals 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 MACEs. However, there was no statistically significant difference in the risk of cardiovascular, all-cause mortality, and stroke[47].

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 MACEs, 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[48].

Additionally, the ongoing SUMMIT 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[49]. 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. Cardiovascular outcome trials are listed in Table 2.

Nephroprotective 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[18].

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 and renal oxidative stress, improving blood pressure, and glycemic control collectively contribute to the anti-albuminuric effects observed with GLP-1 Ras[18].

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[44,45]. 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

Table 2 Cardiovascular outcome trials of glucagon-like peptide-1 and dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonists

Trial name	No. of patients	Study population	Active comparator	Follow-up	Outcomes
LEADER	9340	T2DM, ≥ 50 yr with established CVD, or age ≥ 60 yr with CV risk factors	1.8 mg of liraglutide once-daily SC	3.8 yr	13% reduction in MACEs; 15% reduction in overall mortality; 22% reduction in CV-related deaths
SUSTAIN-6	3297	T2DM, ≥ 50 yr with established CVD, or CKD ≥ stage 3, or age ≥ 60 yr with CV risk factors	0.5 mg or 1.0 mg semaglutide once-weekly SC	2.1 yr	26% reduction in MACEs; 39% reduction in non-fatal stroke
PIONEER 6	3183	T2DM, ≥ 50 yr with established CVD, or CKD ≥ stage 3, or age ≥ 60 yr with CV risk factors	14 mg of semaglutide once-daily oral	1.3 yr	No significant reduction in MACEs; 51% significant reduction in CV-related deaths
AMPLITUDE-O	4076	T2DM, ≥ 50 yr with established CVD, or CKD ≥ stage 3 with CV risk factors	4 or 6 mg of efpeglenatide once-weekly SC	1.81 yr	27% reduction in MACEs; reduced risk of hospitalization for heart failure
HARMONY	9463	T2DM, age ≥ 40 yr with CVD	30-50 mg of albiglutide once-weekly SC	1.6 yr	22% reduction in MACEs
SURPASS-4	2002	T2DM, ≥ 18 yr with established CVD, or with CV risk factors	5 mg, 10 mg, or 15 mg of tirzepatide once-weekly SC	2 yr	Tirzepatide treatment was not associated with increased CV risk

MACEs: Major adverse cardiac events, including cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and hospitalization for unstable angina; CKD: Chronic kidney disease; CV: Cardiovascular; CVD: Cardiovascular disease; T2DM: Type 2 diabetes mellitus; SC: Subcutaneous; LEADER: Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; SUSTAIN-6: Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes 6.

patients with T2DM compared to insulin glargine[48].

Contraindications and precautions for GLP-1 and dual GIP and GLP-1 RA 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[50].

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[51].

Renal impairment: 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[52,53]. 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[54].

Gastroparesis & inflammatory bowel disease: Patients with gastroparesis and inflammatory bowel disease should avoid GLP-1 analogs. It's crucial to acknowledge the absence of precise measurements for gastric emptying using appropriate methodologies when it comes to longer-acting GLP-1 RAs. Moreover, there should be recognition of the suboptimal assessment of gastrointestinal adverse effects relying on self-reported information[55]. Furthermore, the accurate diagnosis of gastroparesis relies on direct measurement, with Scintigraphy remaining the 'gold-standard' technique[56].

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 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[57]. 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 intra-duodenal-jejunal region and inhibiting the migrating motor complex in both healthy individuals and patients[58].

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[35,50,59]. 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[60]. 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 RAs, particularly notable after 1-3 years of treatment duration [61]. 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[62]. Although evidence in human studies remains inconclusive, GLP-1 RAs are contraindicated in patients with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2[35, 62].

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[63,64].

Cost burden of dual GIP and GLP-1 RAs

Cost considerations play a crucial role in the selection of medications 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)[65]. 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[66]. 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[67]. In another United States study, it was demonstrated that once-weekly semaglutide at doses of 0.5 mg and 1.0 mg outperforms exenatide ER and dulaglutide in terms of cost-effectiveness for achieving both individual and combined treatment endpoints. This includes improvements in glycemic control, reduction in body weight, and avoidance of hypoglycemia. Consequently, the study suggests that once-weekly semaglutide at these specified doses presents a favorable economic proposition in the United States, especially for the achievement of comprehensive treatment objectives in individuals with type 2 diabetes[68].

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 rely 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[69].

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[69].

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[70]. 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[34,69,71].

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 7 d after discontinuing the original drug.

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 and 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

Table 3 Suggested equivalent doses for different glucagon-like peptide-1 and dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1 receptor agonists based on their impact on glycemic control

Agent	Route	Frequency	Equivalent dose									
Exenatide	SC	Twice daily	5 μg[1]	10 μg								
Lixisenatide	SC	Daily	10 μg[1]	20 μg								
Liraglutide	SC	Weekly	0.6 mg[1]	1.2 mg	1.8 mg							
Exenatide XR	SC	Weekly			2 mg							
Dulaglutide	SC	Weekly		0.75 mg[1]	1.5 mg	3 mg	4.5 mg					
Semaglutide	SC	Weekly		0.25 mg[1]	0.5 mg		1 mg	2 mg				
Semaglutide	PO	Daily	3 mg[1]	7 mg	14 mg							
Tirzepatide	SC	Weekly			2.5 mg[1]			5 mg	7.5 mg	10 mg	12.5 mg	15 mg

[1]The comparative efficacy of starting doses is not known and is based on the clinical experience of the authors in this group in various settings in different countries.
SC: Subcutaneous; PO: Oral.

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 4 wk[32]. 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 7 d 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[26,72].

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[57]. This phenomenon is believed to be due to the rapid tachyphylaxis at the level of the vagal nerve activation[73,74]. However, the inhibitory effect of GLP-1RAs on gastric emptying might be diminished or absent in patients with diabetic-related dysautonomia[75].

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[76]. 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[57,73,77].

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[26,57,69-73]. 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[76-79].

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[80,81]. 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[80,81]. 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 1 d before surgery on daily doses and 1 wk 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[23,24,26]. However, if a dose of lixisenatide is missed, the missed dose should be

administered 1 h prior to the next meal[25]. For the once-weekly exenatide or dulaglutide, the missed dose should be administered as soon as possible if there are ≥ 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[21-23].

Regarding the injectable once-weekly semaglutide, administration is allowed within 5 d after the missed dose. However, if more than 5 d have passed, the dose can be skipped, and the next scheduled dose can be administered on time[26]. For tirzepatide, administration is done within 4 d after the missed dose. However, if more than 4 d have passed, the dose can be skipped, and the next scheduled dose can be administered on time[27].

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[82]. 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 [83,84]. 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[24,26,27, 79]. Additionally, it is recommended to wait for at least 2 mo before planning pregnancy as a wash-out period in patients using injectable semaglutide[26]. It is important to note that the effectiveness of oral hormonal contraception may decline while a patient is on tirzepatide therapy[27,85]. Lastly, experience with the use of GLP-1 RAs in breastfeeding women is limited; therefore, their use is not recommended during lactation[85].

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-en-Y gastric bypass (RYGB). 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[86]. 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[87]. Another systemic review showed that following RYGB, individuals experiencing post-bariatric surgery hypoglycemia exhibit heightened GLP-1, insulin, and C-peptide in response to nutrients, with lower HbA1c levels. These findings propose that inhibiting GLP-1 could be a reasonable intervention to prevent hypoglycemia in patients dealing with post-bariatric surgery hypoglycemia following RYGB[88]. 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 [89].

In a recent review, semaglutide was deemed a viable treatment option for individuals experiencing weight regain following bariatric surgery[90]. On the other hand, no specific studies have been conducted to evaluate tirzepatide in post-bariatric surgery patients[91]. 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 6 mo 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[92].

In another retrospective observational study involving 50 patients who experienced weight regain after bariatric surgery, the effectiveness of the 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 that 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[93].

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. The majority of the documented cases occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration during GLP-1 RA treatment. Therefore, it is important to monitor the kidney function in patients who are on GLP-1 RAs and complain of severe GI reactions[21-27].

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)[21-27].

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 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

Table 4 Pharmacokinetic properties and renal outcomes of clinical trials with glucagon-like peptide-1 receptor agonists

Drug	Dose	Half-life (h)	Elimination	Clinical study	Renal benefit
Short-acting GLP-1 receptor agonists					
Exenatide	5-10 μg twice-daily SC	2.4	Mostly renal	None	None
Lixisenatide	10-20 μg once-daily SC	3.0	Mostly renal	ELIXA[65]	Lower rate of increase in urinary albumin-to-creatinine ratio
Long-acting GLP-1 receptor agonists					
Exenatide	2 mg QW SC	2.4	Mostly renal		
Liraglutide	0.6 mg, 1.2 mg or 1.8 mg once-daily SC	11.6-13.0	Peptidases and renal 6%; feces 5%	LEADER [64]	Nephropathy was decreased. UACR was decreased. RAS hormone was decreased. Progression to macroalbuminuria was decreased. Doubling of serum creatinine levels was decreased. eGFR of ≤ 45 mL/min per 1.73 m^2 was decreased. The initiation of renal replacement therapy was decreased. Risk of end-stage renal disease or renal death was decreased. Plasma renin concentration, renin activity, and angiotensin II were decreased
Semaglutide	0.5-1.0 mg once-weekly SC	165.0-184.0	Peptidases and renal	SUSTAIN-6[67]	Nephropathy > 35% was decreased. Progression to macroalbuminuria was decreased. Doubling of serum creatinine levels was decreased. eGFR of ≤ 45 mL/min per 1.73 m^2 was decreased. The initiation of renal replacement therapy decreased
Dulaglutide	0.75-1.5 mg once-weekly SC	About 112.8	Peptidases and renal	AWARD VII[66]	Reduced albuminuria, slower decline in renal function
Albiglutide	30-50 mg once-weekly SC	About 120.0	Peptidases and renal	None	None

GLP-1: Glucagon-like peptide-1; SC: Subcutaneous; UACR: Urinary albumin-to-creatinine ratio; RAS: Renin-angiotensin-system; eGFR: Estimated glomerular filtration rate; LEADER: Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; SUSTAIN-6: Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes 6.

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[94].

Another notable trial is the AWARD-7 trial which compared the benefits of the long-acting GLP-1 analog dulaglutide and insulin glargine on kidney function in patients with T2DM and moderate-to-severe chronic kidney disease. The trial involved 577 participants who 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[95]. The pharmacokinetic outcomes and renal benefits of clinical trials with GLP-1 and dual GLP-1/GIP RA agents are shown in Table 4[96].

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[45]. Another possible theory is that it suppresses inflammation-related pathways, thus resulting in anti-inflammatory and antioxidative effects[97].

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[98-102]. GLP-1 RAs have a potential hypoglycemia risk when used with other glucose-lowering agents[103]. 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[99]. 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, and 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)[98-100].

CONCLUSION

The utilization and switching between GLP-1 and dual GLP-1/GIP RAs pose complex challenges in various clinical scenarios, which 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.

FOOTNOTES

Author contributions: Alqifari SF, Alkomi O, and Esmail A contributed to the conceptualization of this study; Alqifari SF and Alkhawami K were involved in the methodology of this review; Yousri S and Muqresh MA participated in the validation of this manuscript; Alharbi N and Khojah AA took part in the formal analysis of this article; Khojah AA and Aljabri A curated the data; Alqifari SF, Alkomi O, Esmail A, Allahham A, Prabahar K, and Alshareef H contributed to the writing-original draft preparation; Alqifari SF, Alkhawami K, Alrabiah A, and AlBishi LA were involved in the writing-review and editing; Alqifari SF, Alharbi N, and AlBishi LA took part in the visualization of this study; Alqifari SF contributed to the supervision; Alqifari SF and Alkomi O were major in the project administration; Alqifari SF and Alrabiah A contributed to the funding acquisition; and all authors have read and agreed to the published version of the manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Country/Territory of origin: Saudi Arabia

ORCID number: Saleh Fahad Alqifari 0000-0002-0288-065X; Omar Alkomi 0000-0001-8537-2521; Abdullah Esmail 0009-0003-7979-5036; Khadijeh Alkhawami 0009-0006-8412-2030; Shahd Yousri 0009-0001-4702-8006; Mohamad Ayham Muqresh 0000-0002-5971-9664; Nawwarah Alharbi 0009-0007-8583-9620; Abdullah A Khojah 0000-0001-9327-8519; Ahmed Aljabri 0000-0002-7049-9826; Abdulrahman Allahham 0000-0003-3155-7314; Kousalya Prabahar 0000-0001-8224-4276; Hanan Alshareef 0000-0002-1264-7229; Mohammed Aldhaeefi 0000-0002-5985-9149; Tariq Alrasheed 0009-0009-8239-5061; Ali Alrabiah 0009-0008-0191-6842; Laila A AlBishi 0000-0002-4677-3581.

S-Editor: Wang JJ
L-Editor: Wang TQ
P-Editor: Zheng XM

REFERENCES

1 **Nauck MA**, Meier JJ. Incretin hormones: Their role in health and disease. *Diabetes Obes Metab* 2018; **20** Suppl 1: 5-21 [PMID: 29364588 DOI: 10.1111/dom.13129]
2 **Sheahan KH**, Wahlberg EA, Gilbert MP. An overview of GLP-1 agonists and recent cardiovascular outcomes trials. *Postgrad Med J* 2020; **96**: 156-161 [PMID: 31801807 DOI: 10.1136/postgradmedj-2019-137186]
3 **Mathiesen DS**, Bagger JI, Bergmann NC, Lund A, Christensen MB, Vilsbøll T, Knop FK. The Effects of Dual GLP-1/GIP Receptor Agonism on Glucagon Secretion-A Review. *Int J Mol Sci* 2019; **20** [PMID: 31443356 DOI: 10.3390/ijms20174092]
4 **Campbell JE**, Drucker DJ. Pharmacology, physiology, and mechanisms of incretin hormone action. *Cell Metab* 2013; **17**: 819-837 [PMID: 23684623 DOI: 10.1016/j.cmet.2013.04.008]
5 **Stevens JE**, Jalleh RJ, Trahair LG, Marathe CS, Horowitz M, Jones KL. Comparative effects of low-carbohydrate, full-strength and low-alcohol beer on gastric emptying, alcohol absorption, glycaemia and insulinaemia in health. *Br J Clin Pharmacol* 2022; **88**: 3421-3427 [PMID: 35246999 DOI: 10.1111/bcp.15297]
6 **DeFronzo RA**, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care* 2005; **28**: 1092-1100 [PMID: 15855572 DOI: 10.2337/diacare.28.5.1092]
7 **Palmer SC**, Tendal B, Mustafa RA, Vandvik PO, Li S, Hao Q, Tunnicliffe D, Ruospo M, Natale P, Saglimbene V, Nicolucci A, Johnson DW, Tonelli M, Rossi MC, Badve SV, Cho Y, Nadeau-Fredette AC, Burke M, Faruque LI, Lloyd A, Ahmad N, Liu Y, Tiv S, Millard T, Gagliardi L, Kolanu N, Barmanray RD, McMorrow R, Raygoza Cortez AK, White H, Chen X, Zhou X, Liu J, Rodríguez AF, González-Colmenero AD, Wang Y, Li L, Sutanto S, Solis RC, Díaz González-Colmenero F, Rodriguez-Gutierrez R, Walsh M, Guyatt G, Strippoli GFM. Sodium-glucose

cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials. *BMJ* 2021; **372**: m4573 [PMID: 33441402 DOI: 10.1136/bmj.m4573]

8 **Iqbal J**, Wu HX, Hu N, Zhou YH, Li L, Xiao F, Wang T, Jiang HL, Xu SN, Huang BL, Zhou HD. Effect of glucagon-like peptide-1 receptor agonists on body weight in adults with obesity without diabetes mellitus-a systematic review and meta-analysis of randomized control trials. *Obes Rev* 2022; **23**: e13435 [PMID: 35194917 DOI: 10.1111/obr.13435]

9 **Jepsen MM**, Christensen MB. Emerging glucagon-like peptide 1 receptor agonists for the treatment of obesity. *Expert Opin Emerg Drugs* 2021; **26**: 231-243 [PMID: 34176426 DOI: 10.1080/14728214.2021.1947240]

10 **Karagiannis T**, Avgerinos I, Liakos A, Del Prato S, Matthews DR, Tsapas A, Bekiari E. Management of type 2 diabetes with the dual GIP/GLP-1 receptor agonist tirzepatide: a systematic review and meta-analysis. *Diabetologia* 2022; **65**: 1251-1261 [PMID: 35579691 DOI: 10.1007/s00125-022-05715-4]

11 **Willard FS**, Douros JD, Gabe MB, Showalter AD, Wainscott DB, Suter TM, Capozzi ME, van der Velden WJ, Stutsman C, Cardona GR, Urva S, Emmerson PJ, Holst JJ, D'Alessio DA, Coghlan MP, Rosenkilde MM, Campbell JE, Sloop KW. Tirzepatide is an imbalanced and biased dual GIP and GLP-1 receptor agonist. *JCI Insight* 2020; **5** [PMID: 32730231 DOI: 10.1172/jci.insight.140532]

12 **Lin F**, Yu B, Ling B, Lv G, Shang H, Zhao X, Jie X, Chen J, Li Y. Weight loss efficiency and safety of tirzepatide: A Systematic review. *PLoS One* 2023; **18**: e0285197 [PMID: 37141329 DOI: 10.1371/journal.pone.0285197]

13 **Thomas MK**, Nikooienejad A, Bray R, Cui X, Wilson J, Duffin K, Milicevic Z, Haupt A, Robins DA. Dual GIP and GLP-1 Receptor Agonist Tirzepatide Improves Beta-cell Function and Insulin Sensitivity in Type 2 Diabetes. *J Clin Endocrinol Metab* 2021; **106**: 388-396 [PMID: 33236115 DOI: 10.1210/clinem/dgaa863]

14 **Buse JB**, Wexler DJ, Tsapas A, Rossing P, Mingrone G, Mathieu C, D'Alessio DA, Davies MJ. 2019 Update to: Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2020; **43**: 487-493 [PMID: 31857443 DOI: 10.2337/dci19-0066]

15 **Davies MJ**, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, Rossing P, Tsapas A, Wexler DJ, Buse JB. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2018; **41**: 2669-2701 [PMID: 30291106 DOI: 10.2337/dci18-0033]

16 **Garber AJ**, Handelsman Y, Grunberger G, Einhorn D, Abrahamson MJ, Barzilay JI, Blonde L, Bush MA, DeFronzo RA, Garber JR, Garvey WT, Hirsch IB, Jellinger PS, McGill JB, Mechanick JI, Perreault L, Rosenblit PD, Samson S, Umpierrez GE. CONSENSUS STATEMENT BY THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY ON THE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM - 2020 EXECUTIVE SUMMARY. *Endocr Pract* 2020; **26**: 107-139 [PMID: 32022600 DOI: 10.4158/CS-2019-0472]

17 **Ma X**, Liu Z, Ilyas I, Little PJ, Kamato D, Sahebka A, Chen Z, Luo S, Zheng X, Weng J, Xu S. GLP-1 receptor agonists (GLP-1RAs): cardiovascular actions and therapeutic potential. *Int J Biol Sci* 2021; **17**: 2050-2068 [PMID: 34131405 DOI: 10.7150/ijbs.59965]

18 **Greco EV**, Russo G, Giandalia A, Viazzi F, Pontremoli R, De Cosmo S. GLP-1 Receptor Agonists and Kidney Protection. *Medicina (Kaunas)* 2019; **55** [PMID: 31159279 DOI: 10.3390/medicina55060233]

19 **Zoungas S**, Arima H, Gerstein HC, Holman RR, Woodward M, Reaven P, Hayward RA, Craven T, Coleman RL, Chalmers J; Collaborators on Trials of Lowering Glucose (CONTROL) group. Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual participant data from randomised controlled trials. *Lancet Diabetes Endocrinol* 2017; **5**: 431-437 [PMID: 28365411 DOI: 10.1016/S2213-8587(17)30104-3]

20 **Drucker DJ**. Mechanisms of Action and Therapeutic Application of Glucagon-like Peptide-1. *Cell Metab* 2018; **27**: 740-756 [PMID: 29617641 DOI: 10.1016/j.cmet.2018.03.001]

21 Dulaglutide (package insert). [cited 13 August 2023]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125469s036lbl.pdf

22 Exenatide (package insert). [cited 13 August 2023]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021773s9s11s18s22s25lbl.pdf

23 Exenatide extended release (package insert). [cited 13 August 2023]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022200s026lbl.pdf

24 Liraglutide (package insert). [cited 13 August 2023]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022341s027lbl.pdf

25 Lixisenatide (package insert). [cited 13 August 2023]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208471orig1s000lbl.pdf

26 Semaglutide (package insert). [cited 13 August 2023]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209637lbl.pdf

27 Tirzepatide (package insert). [cited 13 August 2023]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215866s000lbl.pdf

28 **Nauck MA**, Meier JJ. The incretin effect in healthy individuals and those with type 2 diabetes: physiology, pathophysiology, and response to therapeutic interventions. *Lancet Diabetes Endocrinol* 2016; **4**: 525-536 [PMID: 26876794 DOI: 10.1016/S2213-8587(15)00482-9]

29 **Chavda VP**, Ajabiya J, Teli D, Bojarska J, Apostolopoulos V. Tirzepatide, a New Era of Dual-Targeted Treatment for Diabetes and Obesity: A Mini-Review. *Molecules* 2022; **27** [PMID: 35807558 DOI: 10.3390/molecules27134315]

30 **Dahl D**, Onishi Y, Norwood P, Huh R, Bray R, Patel H, Rodríguez Á. Effect of Subcutaneous Tirzepatide vs Placebo Added to Titrated Insulin Glargine on Glycemic Control in Patients With Type 2 Diabetes: The SURPASS-5 Randomized Clinical Trial. *JAMA* 2022; **327**: 534-545 [PMID: 35133415 DOI: 10.1001/jama.2022.0078]

31 **Husain M**, Birkenfeld AL, Donsmark M, Dungan K, Eliaschewitz FG, Franco DR, Jeppesen OK, Lingvay I, Mosenzon O, Pedersen SD, Tack CJ, Thomsen M, Vilsbøll T, Warren ML, Bain SC; PIONEER 6 Investigators. Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med* 2019; **381**: 841-851 [PMID: 31185157 DOI: 10.1056/NEJMoa1901118]

32 **Frías JP**, Davies MJ, Rosenstock J, Pérez Manghi FC, Fernández Landó L, Bergman BK, Liu B, Cui X, Brown K; SURPASS-2 Investigators. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. *N Engl J Med* 2021; **385**: 503-515 [PMID: 34170647 DOI: 10.1056/NEJMoa2107519]

33 **GRADE Study Research Group**, Nathan DM, Lachin JM, Bebu I, Burch HB, Buse JB, Cherrington AL, Fortmann SP, Green JB, Kahn SE, Kirkman MS, Krause-Steinrauf H, Larkin ME, Phillips LS, Pop-Busui R, Steffes M, Tiktin M, Tripputi M, Wexler DJ, Younes N. Glycemia

Reduction in Type 2 Diabetes - Microvascular and Cardiovascular Outcomes. *N Engl J Med* 2022; **387**: 1075-1088 [PMID: 36129997 DOI: 10.1056/NEJMoa2200436]

34 **Eli Lilly and Company**. A study to evaluate tirzepatide (LY3298176) in pediatric and adolescent participants with type 2 diabetes mellitus inadequately controlled with metformin or basal insulin or both - full text view. [accessed 2023 Oct 17]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT05260021 ClinicalTrials.gov Identifier: NCT05260021

35 **Collins L**, Costello RA. Glucagon-Like Peptide-1 Receptor Agonists. 2023 Jan 13. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan- [PMID: 31855395]

36 **Maideen NM**. Pharmacologically relevant drug interactions of glucagon-like peptide-1 receptor agonists. *J Anal Pharm Res* 2019; **8**: 51-53 [DOI: 10.15406/japlr.2019.08.00311]

37 **Sun F**, Wu S, Guo S, Yu K, Yang Z, Li L, Zhang Y, Quan X, Ji L, Zhan S. Impact of GLP-1 receptor agonists on blood pressure, heart rate and hypertension among patients with type 2 diabetes: A systematic review and network meta-analysis. *Diabetes Res Clin Pract* 2015; **110**: 26-37 [PMID: 26358202 DOI: 10.1016/j.diabres.2015.07.015]

38 **Pujadas G**, Drucker DJ. Vascular Biology of Glucagon Receptor Superfamily Peptides: Mechanistic and Clinical Relevance. *Endocr Rev* 2016; **37**: 554-583 [PMID: 27732058 DOI: 10.1210/er.2016-1078]

39 **Lovshin JA**, Barnie A, DeAlmeida A, Logan A, Zinman B, Drucker DJ. Liraglutide promotes natriuresis but does not increase circulating levels of atrial natriuretic peptide in hypertensive subjects with type 2 diabetes. *Diabetes Care* 2015; **38**: 132-139 [PMID: 25414155 DOI: 10.2337/dc14-1958]

40 **Hogan AE**, Gaoatswe G, Lynch L, Corrigan MA, Woods C, O'Connell J, O'Shea D. Glucagon-like peptide 1 analogue therapy directly modulates innate immune-mediated inflammation in individuals with type 2 diabetes mellitus. *Diabetologia* 2014; **57**: 781-784 [PMID: 24362727 DOI: 10.1007/s00125-013-3145-0]

41 **Nauck MA**, Meier JJ, Cavender MA, Abd El Aziz M, Drucker DJ. Cardiovascular Actions and Clinical Outcomes With Glucagon-Like Peptide-1 Receptor Agonists and Dipeptidyl Peptidase-4 Inhibitors. *Circulation* 2017; **136**: 849-870 [PMID: 28847797 DOI: 10.1161/CIRCULATIONAHA.117.028136]

42 **Helmstädter J**, Frenis K, Filippou K, Grill A, Dib M, Kalinovic S, Pawelke F, Kus K, Kröller-Schön S, Oelze M, Chlopicki S, Schuppan D, Wenzel P, Ruf W, Drucker DJ, Münzel T, Daiber A, Steven S. Endothelial GLP-1 (Glucagon-Like Peptide-1) Receptor Mediates Cardiovascular Protection by Liraglutide In Mice With Experimental Arterial Hypertension. *Arterioscler Thromb Vasc Biol* 2020; **40**: 145-158 [PMID: 31747801 DOI: 10.1161/atv.0000615456.97862.30]

43 **Barale C**, Buracco S, Cavalot F, Frascaroli C, Guerrasio A, Russo I. Glucagon-like peptide 1-related peptides increase nitric oxide effects to reduce platelet activation. *Thromb Haemost* 2017; **117**: 1115-1128 [PMID: 28405672 DOI: 10.1160/TH16-07-0586]

44 **Marso SP**, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2016; **375**: 311-322 [PMID: 27295427 DOI: 10.1056/NEJMoa1603827]

45 **Marso SP**, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, Woo V, Hansen O, Holst AG, Pettersson J, Vilsbøll T; SUSTAIN-6 Investigators. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med* 2016; **375**: 1834-1844 [PMID: 27633186 DOI: 10.1056/NEJMoa1607141]

46 **Gerstein HC**, Sattar N, Rosenstock J, Ramasundarahettige C, Pratley R, Lopes RD, Lam CSP, Khurmi NS, Heenan L, Del Prato S, Dyal L, Branch K; AMPLITUDE-O Trial Investigators. Cardiovascular and Renal Outcomes with Efpeglenatide in Type 2 Diabetes. *N Engl J Med* 2021; **385**: 896-907 [PMID: 34215025 DOI: 10.1056/NEJMoa2108269]

47 **Green JB**, Hernandez AF, D'Agostino RB, Granger CB, Janmohamed S, Jones NP, Leiter LA, Noronha D, Russell R, Sigmon K, Del Prato S, McMurray JJV. Harmony Outcomes: A randomized, double-blind, placebo-controlled trial of the effect of albiglutide on major cardiovascular events in patients with type 2 diabetes mellitus-Rationale, design, and baseline characteristics. *Am Heart J* 2018; **203**: 30-38 [PMID: 30015066 DOI: 10.1016/j.ahj.2018.03.030]

48 **Del Prato S**, Kahn SE, Pavo I, Weerakkody GJ, Yang Z, Doupis J, Aizenberg D, Wynne AG, Riesmeyer JS, Heine RJ, Wiese RJ; SURPASS-4 Investigators. Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial. *Lancet* 2021; **398**: 1811-1824 [PMID: 34672967 DOI: 10.1016/S0140-6736(21)02188-7]

49 **Eli Lilly and Company**. A study of Tirzepatide (LY3298176) in participants with heart failure with preserved ejection fraction and obesity - full text view. [accessed 2023 Oct 23]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT04847557 ClinicalTrials.gov Identifier: NCT04847557

50 **Elashoff M**, Matveyenko AV, Gier B, Elashoff R, Butler PC. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. *Gastroenterology* 2011; **141**: 150-156 [PMID: 21334333 DOI: 10.1053/j.gastro.2011.02.018]

51 **Dandona P**, Chaudhuri A, Ghanim H. Semaglutide in Early Type 1 Diabetes. *N Engl J Med* 2023; **389**: 958-959 [PMID: 37672701 DOI: 10.1056/NEJMc2302677]

52 **Sanofi**. Lyxumia (lixisenatide) summary of product characteristics. 2014. [cited 20 August 2023]. Available from: https://www.ema.europa.eu/en/documents/product-information/lyxumia-epar-product-information_en.pdf

53 **GlaxoSmithKline**. Eperzan (albiglutide) summary of product characteristics. 2015. [cited 20 August 2023]. Available from: https://www.ema.europa.eu/en/documents/product-information/eperzan-epar-product-information_en.pdf

54 **Urva S**, Quinlan T, Landry J, Martin J, Loghin C. Effects of Renal Impairment on the Pharmacokinetics of the Dual GIP and GLP-1 Receptor Agonist Tirzepatide. *Clin Pharmacokinet* 2021; **60**: 1049-1059 [PMID: 33778934 DOI: 10.1007/s40262-021-01012-2]

55 **Jalleh RJ**, Jones KL, Nauck M, Horowitz M. Accurate Measurements of Gastric Emptying and Gastrointestinal Symptoms in the Evaluation of Glucagon-like Peptide-1 Receptor Agonists. *Ann Intern Med* 2023; **176**: 1542-1543 [PMID: 37931267 DOI: 10.7326/M23-2019]

56 **Jalleh RJ**, Jones KL, Rayner CK, Marathe CS, Wu T, Horowitz M. Normal and disordered gastric emptying in diabetes: recent insights into (patho)physiology, management and impact on glycaemic control. *Diabetologia* 2022; **65**: 1981-1993 [PMID: 36194250 DOI: 10.1007/s00125-022-05796-1]

57 **Marathe CS**, Rayner CK, Jones KL, Horowitz M. Effects of GLP-1 and incretin-based therapies on gastrointestinal motor function. *Exp Diabetes Res* 2011; **2011**: 279530 [PMID: 21747825 DOI: 10.1155/2011/279530]

58 **Hellström PM**, Näslund E, Edholm T, Schmidt PT, Kristensen J, Theodorsson E, Holst JJ, Efendic S. GLP-1 suppresses gastrointestinal motility and inhibits the migrating motor complex in healthy subjects and patients with irritable bowel syndrome. *Neurogastroenterol Motil* 2008; **20**: 649-659 [PMID: 18298441 DOI: 10.1111/j.1365-2982.2007.01079.x]

59 **Gier B**, Butler PC, Lai CK, Kirakossian D, DeNicola MM, Yeh MW. Glucagon like peptide-1 receptor expression in the human thyroid gland. *J Clin Endocrinol Metab* 2012; **97**: 121-131 [PMID: 22031513 DOI: 10.1210/jc.2011-2407]

60 **He L**, Zhang S, Zhang X, Liu R, Guan H, Zhang H. Effects of insulin analogs and glucagon-like peptide-1 receptor agonists on proliferation and cellular energy metabolism in papillary thyroid cancer. *Onco Targets Ther* 2017; **10**: 5621-5631 [PMID: 29200876 DOI: 10.2147/OTT.S150701]

61 **Bezin J**, Gouverneur A, Pénichon M, Mathieu C, Garrel R, Hillaire-Buys D, Pariente A, Faillie JL. GLP-1 Receptor Agonists and the Risk of Thyroid Cancer. *Diabetes Care* 2023; **46**: 384-390 [PMID: 36356111 DOI: 10.2337/dc22-1148]

62 **Hu W**, Song R, Cheng R, Liu C, Guo R, Tang W, Zhang J, Zhao Q, Li X, Liu J. Use of GLP-1 Receptor Agonists and Occurrence of Thyroid Disorders: a Meta-Analysis of Randomized Controlled Trials. *Front Endocrinol (Lausanne)* 2022; **13**: 927859 [PMID: 35898463 DOI: 10.3389/fendo.2022.927859]

63 **Woronow D**, Chamberlain C, Niak A, Avigan M, Houstoun M, Kortepeter C. Acute Cholecystitis Associated With the Use of Glucagon-Like Peptide-1 Receptor Agonists Reported to the US Food and Drug Administration. *JAMA Intern Med* 2022; **182**: 1104-1106 [PMID: 36036939 DOI: 10.1001/jamainternmed.2022.3810]

64 **Vilsbøll T**, Bain SC, Leiter LA, Lingvay I, Matthews D, Simó R, Helmark IC, Wijayasinghe N, Larsen M. Semaglutide, reduction in glycated haemoglobin and the risk of diabetic retinopathy. *Diabetes Obes Metab* 2018; **20**: 889-897 [PMID: 29178519 DOI: 10.1111/dom.13172]

65 **Alkhatib NS**, Almutairi AR, Alkhezi OS, Alfayez OM, Al Yami MS, Almohammed OA. Economic analysis of glucagon like peptide-1 receptor agonists from the Saudi Arabia payer perspective. *Saudi Pharm J* 2022; **30**: 433-439 [PMID: 35527835 DOI: 10.1016/j.jsps.2022.01.018]

66 **Yang CY**, Chen YR, Ou HT, Kuo S. Cost-effectiveness of GLP-1 receptor agonists versus insulin for the treatment of type 2 diabetes: a real-world study and systematic review. *Cardiovasc Diabetol* 2021; **20**: 21 [PMID: 33468131 DOI: 10.1186/s12933-020-01211-4]

67 **Mody R**, Huang Q, Yu M, Zhao R, Patel H, Grabner M, Landó LF. Adherence, persistence, glycaemic control and costs among patients with type 2 diabetes initiating dulaglutide compared with liraglutide or exenatide once weekly at 12-month follow-up in a real-world setting in the United States. *Diabetes Obes Metab* 2019; **21**: 920-929 [PMID: 30520248 DOI: 10.1111/dom.13603]

68 **Johansen P**, Hunt B, Iyer NN, Dang-Tan T, Pollock RF. A Relative Cost of Control Analysis of Once-Weekly Semaglutide Versus Exenatide Extended-Release and Dulaglutide for Bringing Patients to HbA1c and Weight Loss Treatment Targets in the USA. *Adv Ther* 2019; **36**: 1190-1199 [PMID: 30875029 DOI: 10.1007/s12325-019-00915-8]

69 **Almandoz JP**, Lingvay I, Morales J, Campos C. Switching Between Glucagon-Like Peptide-1 Receptor Agonists: Rationale and Practical Guidance. *Clin Diabetes* 2020; **38**: 390-402 [PMID: 33132510 DOI: 10.2337/cd19-0100]

70 **Hinnen D**. Glucagon-Like Peptide 1 Receptor Agonists for Type 2 Diabetes. *Diabetes Spectr* 2017; **30**: 202-210 [PMID: 28848315 DOI: 10.2337/ds16-0026]

71 **Jain AB**, Ali A, Gorgojo Martínez JJ, Hramiak I, Kavia K, Madsbad S, Potier L, Prohaska BD, Strong JL, Vilsbøll T. Switching between GLP-1 receptor agonists in clinical practice: Expert consensus and practical guidance. *Int J Clin Pract* 2021; **75**: e13731 [PMID: 32975890 DOI: 10.1111/ijcp.13731]

72 **Whitley HP**, Trujillo JM, Neumiller JJ. Special Report: Potential Strategies for Addressing GLP-1 and Dual GLP-1/GIP Receptor Agonist Shortages. *Clin Diabetes* 2023; **41**: 467-473 [PMID: 37456085 DOI: 10.2337/cd23-0023]

73 **Tong J**, D'Alessio D. Give the receptor a brake: slowing gastric emptying by GLP-1. *Diabetes* 2014; **63**: 407-409 [PMID: 24464721 DOI: 10.2337/db13-1764]

74 **Nauck MA**, Kemmeries G, Holst JJ, Meier JJ. Rapid tachyphylaxis of the glucagon-like peptide 1-induced deceleration of gastric emptying in humans. *Diabetes* 2011; **60**: 1561-1565 [PMID: 21430088 DOI: 10.2337/db10-0474]

75 **Nakatani Y**, Maeda M, Matsumura M, Shimizu R, Banba N, Aso Y, Yasu T, Harasawa H. Effect of GLP-1 receptor agonist on gastrointestinal tract motility and residue rates as evaluated by capsule endoscopy. *Diabetes Metab* 2017; **43**: 430-437 [PMID: 28648835 DOI: 10.1016/j.diabet.2017.05.009]

76 **Maselli D**, Atieh J, Clark MM, Eckert D, Taylor A, Carlson P, Burton DD, Busciglio I, Harmsen WS, Vella A, Acosta A, Camilleri M. Effects of liraglutide on gastrointestinal functions and weight in obesity: A randomized clinical and pharmacogenomic trial. *Obesity (Silver Spring)* 2022; **30**: 1608-1620 [PMID: 35894080 DOI: 10.1002/oby.23481]

77 **Jones KL**, Huynh LQ, Hatzinikolas S, Rigda RS, Phillips LK, Pham HT, Marathe CS, Wu T, Malbert CH, Stevens JE, Lange K, Rayner CK, Horowitz M. Exenatide once weekly slows gastric emptying of solids and liquids in healthy, overweight people at steady-state concentrations. *Diabetes Obes Metab* 2020; **22**: 788-797 [PMID: 31903712 DOI: 10.1111/dom.13956]

78 **Linnebjerg H**, Park S, Kothare PA, Trautmann ME, Mace K, Fineman M, Wilding I, Nauck M, Horowitz M. Effect of exenatide on gastric emptying and relationship to postprandial glycemia in type 2 diabetes. *Regul Pept* 2008; **151**: 123-129 [PMID: 18675854 DOI: 10.1016/j.regpep.2008.07.003]

79 **Watson LE**, Xie C, Wang X, Li Z, Phillips LK, Sun Z, Jones KL, Horowitz M, Rayner CK, Wu T. Gastric Emptying in Patients With Well-Controlled Type 2 Diabetes Compared With Young and Older Control Subjects Without Diabetes. *J Clin Endocrinol Metab* 2019; **104**: 3311-3319 [PMID: 30933282 DOI: 10.1210/jc.2018-02736]

80 **Klein SR**, Hobai IA. Semaglutide, delayed gastric emptying, and intraoperative pulmonary aspiration: a case report. *Can J Anaesth* 2023; **70**: 1394-1396 [PMID: 36977934 DOI: 10.1007/s12630-023-02440-3]

81 **Silveira SQ**, da Silva LM, de Campos Vieira Abib A, de Moura DTH, de Moura EGH, Santos LB, Ho AM, Nersessian RSF, Lima FLM, Silva MV, Mizubuti GB. Relationship between perioperative semaglutide use and residual gastric content: A retrospective analysis of patients undergoing elective upper endoscopy. *J Clin Anesth* 2023; **87**: 111091 [PMID: 36870274 DOI: 10.1016/j.jclinane.2023.111091]

82 **Muller DRP**, Stenvers DJ, Malekzadeh A, Holleman F, Painter RC, Siegelaar SE. Effects of GLP-1 agonists and SGLT2 inhibitors during pregnancy and lactation on offspring outcomes: a systematic review of the evidence. *Front Endocrinol (Lausanne)* 2023; **14**: 1215356 [PMID: 37881498 DOI: 10.3389/fendo.2023.1215356]

83 **Greco D**. Normal pregnancy outcome after first-trimester exposure to liraglutide in a woman with Type 2 diabetes. *Diabet Med* 2015; **32**: e29-e30 [PMID: 25683470 DOI: 10.1111/dme.12726]

84 **Skov K**, Mandic IN, Nyborg KM. Semaglutide and pregnancy. *Int J Gynaecol Obstet* 2023; **163**: 699-700 [PMID: 37688299 DOI: 10.1002/ijgo.15092]

85 **Chaplin S**, Bain S. Properties of GLP-1 agonists and their use in type 2 diabetes. *Prescriber* 2016; 43-46

86 **Llewellyn DC**, Logan Ellis H, Aylwin SJB, Oštarijaš E, Green S, Sheridan W, Chew NWS, le Roux CW, Miras AD, Patel AG, Vincent RP, Dimitriadis GK. The efficacy of GLP-1RAs for the management of postprandial hypoglycemia following bariatric surgery: a systematic

review. *Obesity (Silver Spring)* 2023; **31**: 20-30 [PMID: 36502288 DOI: 10.1002/oby.23600]

87 **Smith EP**, Polanco G, Yaqub A, Salehi M. Altered glucose metabolism after bariatric surgery: What's GLP-1 got to do with it? *Metabolism* 2018; **83**: 159-166 [PMID: 29113813 DOI: 10.1016/j.metabol.2017.10.014]

88 **Jalleh RJ**, Umapathysivam MM, Plummer MP, Deane A, Jones KL, Horowitz M. Postprandial plasma GLP-1 levels are elevated in individuals with postprandial hypoglycaemia following Roux-en-Y gastric bypass - a systematic review. *Rev Endocr Metab Disord* 2023; **24**: 1075-1088 [PMID: 37439960 DOI: 10.1007/s11154-023-09823-3]

89 **Faurschou A**, Zachariae C, Skov L, Vilsbøll T, Knop FK. Gastric bypass surgery: improving psoriasis through a GLP-1-dependent mechanism? *Med Hypotheses* 2011; **77**: 1098-1101 [PMID: 21968278 DOI: 10.1016/j.mehy.2011.09.011]

90 **Redmond IP**, Shukla AP, Aronne LJ. Use of Weight Loss Medications in Patients after Bariatric Surgery. *Curr Obes Rep* 2021; **10**: 81-89 [PMID: 33492629 DOI: 10.1007/s13679-021-00425-1]

91 **Lautenbach A**, Wernecke M, Huber TB, Stoll F, Wagner J, Meyhöfer SM, Meyhöfer S, Aberle J. The Potential of Semaglutide Once-Weekly in Patients Without Type 2 Diabetes with Weight Regain or Insufficient Weight Loss After Bariatric Surgery-a Retrospective Analysis. *Obes Surg* 2022; **32**: 3280-3288 [PMID: 35879524 DOI: 10.1007/s11695-022-06211-9]

92 **Jensen AB**, Renström F, Aczél S, Folie P, Biraima-Steinemann M, Beuschlein F, Bilz S. Efficacy of the Glucagon-Like Peptide-1 Receptor Agonists Liraglutide and Semaglutide for the Treatment of Weight Regain After Bariatric surgery: a Retrospective Observational Study. *Obes Surg* 2023; **33**: 1017-1025 [PMID: 36765019 DOI: 10.1007/s11695-023-06484-8]

93 **Rubino DM**, Greenway FL, Khalid U, O'Neil PM, Rosenstock J, Sørrig R, Wadden TA, Wizert A, Garvey WT; STEP 8 Investigators. Effect of Weekly Subcutaneous Semaglutide vs Daily Liraglutide on Body Weight in Adults With Overweight or Obesity Without Diabetes: The STEP 8 Randomized Clinical Trial. *JAMA* 2022; **327**: 138-150 [PMID: 35015037 DOI: 10.1001/jama.2021.23619]

94 **Davies MJ**, Bain SC, Atkin SL, Rossing P, Scott D, Shamkhalova MS, Bosch-Traberg H, Syrén A, Umpierrez GE. Efficacy and Safety of Liraglutide Versus Placebo as Add-on to Glucose-Lowering Therapy in Patients With Type 2 Diabetes and Moderate Renal Impairment (LIRA-RENAL): A Randomized Clinical Trial. *Diabetes Care* 2016; **39**: 222-230 [PMID: 26681713 DOI: 10.2337/dc14-2883]

95 **de Vos LC**, Hettige TS, Cooper ME. New Glucose-Lowering Agents for Diabetic Kidney Disease. *Adv Chronic Kidney Dis* 2018; **25**: 149-157 [PMID: 29580579 DOI: 10.1053/j.ackd.2018.01.002]

96 **Ninčević V**, Omanović Kolarić T, Roguljić H, Kizivat T, Smolić M, Bilić Ćurčić I. Renal Benefits of SGLT 2 Inhibitors and GLP-1 Receptor Agonists: Evidence Supporting a Paradigm Shift in the Medical Management of Type 2 Diabetes. *Int J Mol Sci* 2019; **20** [PMID: 31757028 DOI: 10.3390/ijms20235831]

97 **Fujita H**, Morii T, Fujishima H, Sato T, Shimizu T, Hosoba M, Tsukiyama K, Narita T, Takahashi T, Drucker DJ, Seino Y, Yamada Y. The protective roles of GLP-1R signaling in diabetic nephropathy: possible mechanism and therapeutic potential. *Kidney Int* 2014; **85**: 579-589 [PMID: 24152968 DOI: 10.1038/ki.2013.427]

98 **Hassanein MM**, Sahay R, Hafidh K, Djaballah K, Li H, Azar S, Shehadeh N, Hanif W. Safety of lixisenatide versus sulfonylurea added to basal insulin treatment in people with type 2 diabetes mellitus who elect to fast during Ramadan (LixiRam): An international, randomized, open-label trial. *Diabetes Res Clin Pract* 2019; **150**: 331-341 [PMID: 30772385 DOI: 10.1016/j.diabres.2019.01.035]

99 **Ibrahim M**, Davies MJ, Ahmad E, Annabi FA, Eckel RH, Ba-Essa EM, El Sayed NA, Hess Fischl A, Houeiss P, Iraqi H, Khochtali I, Khunti K, Masood SN, Mimouni-Zerguini S, Shera S, Tuomilehto J, Umpierrez GE. Recommendations for management of diabetes during Ramadan: update 2020, applying the principles of the ADA/EASD consensus. *BMJ Open Diabetes Res Care* 2020; **8** [PMID: 32366501 DOI: 10.1136/bmjdrc-2020-001248]

100 **Brady EM**, Davies MJ, Gray LJ, Saeed MA, Smith D, Hanif W, Khunti K. A randomized controlled trial comparing the GLP-1 receptor agonist liraglutide to a sulphonylurea as add on to metformin in patients with established type 2 diabetes during Ramadan: the Treat 4 Ramadan Trial. *Diabetes Obes Metab* 2014; **16**: 527-536 [PMID: 24373063 DOI: 10.1111/dom.12249]

101 **Bashier AM**, Abdulaziz Khalifa A, El Rashid AO. Safety and Efficacy of Liraglutide as an Add-On Therapy to Pre-Existing Anti- Diabetic Regimens during Ramadan, A Prospective Observational Trial. *J Diabetes Metabol* 2015 [DOI: 10.4172/2155-6156.1000590]

102 **Azar ST**, Echtay A, Wan Bebakar WM, Al Araj S, Berrah A, Omar M, Mutha A, Tornøe K, Kaltoft MS, Shehadeh N. Efficacy and safety of liraglutide compared to sulphonylurea during Ramadan in patients with type 2 diabetes (LIRA-Ramadan): a randomized trial. *Diabetes Obes Metab* 2016; **18**: 1025-1033 [PMID: 27376711 DOI: 10.1111/dom.12733]

103 **Amori RE**, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. *JAMA* 2007; **298**: 194-206 [PMID: 17622601 DOI: 10.1001/jama.298.2.194]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: office@baishideng.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com