

A review of glycemic efficacy of liraglutide once daily in achieving glycated hemoglobin targets compared with exenatide twice daily, or sitagliptin once daily in the treatment of type 2 diabetes

Khalid Z. Alshali, MBChB, FRCPC, Abdullah M. Karawagh, MBChB, FRCPC.

ABSTRACT

لقد صارت العلاجات القائمة على إنكريتين مثل ناهضات مستقبلات الببتيد الأول الشبيه بالغلوكاجون ومثبطات الببتيديز الرابع ثنائي الببتيديل واعدة في السنوات الأخيرة لعلاج النوع الثاني من داء السكري. تقدم مثل هذه العلاجات إمكانية تنبيه نشاط الإنسولين داخلي المنشأ بالتناسب مع مستويات الغلوكوز في الدورة الدموية، وهو ما يخفف من خطر نوبات نقص الغلوكوز في الدم. كان كل من ناهض مستقبلات الببتيد الأول الشبيه بالغلوكاجون الصناعي سيتاجليبتين المسمى إكسيناتيد، وناهض مستقبلات الببتيد الأول الشبيه بالغلوكاجون البشري المسمى ليراغلو تيد، ومثبط الببتيديز الرابع ثنائي الببتيديل المسمى سيتاغليبتين هي العقاقير الأولى في أصنافهم التي تحصل على الموافقة لاستخدامها في علاج النوع الثاني من داء السكري وقد جرت دراسة فعاليتها وسلامتها بصورة مكثفة في التجارب السريرية. راجعت هذه المقالة فاعلية ليراغلو تيد مرة يومياً في تحقيق المستويات التي توصي بها الإرشادات للهيوموجلوبين السكري في مرضى النوع الثاني من داء السكري، وذلك بالمقارنة بعقار إكسيناتيد مرتين يومياً أو سيتاغليبتين مرة يومياً، بناءً على المواد المنشورة، وذلك بهدف تسويق الخيار الأفضل للعلاج القائم على إنكريتين في علاج النوع الثاني غير المنضبط من داء السكري.

Incretin-based therapies such as glucagon-like peptide-1 (GLP-1) receptor agonists (RA) and dipeptidyl peptidase-4 (DPP-4) inhibitors have gained prominence in recent years for the treatment of type 2 diabetes (T2D). Such therapies offer the potential to stimulate endogenous insulin activity in proportion to circulating glucose levels; thereby, lowering the risk of hypoglycemic episodes. The synthetic GLP-1 RA exenatide, the human GLP-1 RA liraglutide, and the DPP-4 inhibitor sitagliptin are the first agents in their respective classes to be approved for the treatment of T2D and their efficacy and safety has been studied extensively in clinical trials. This article reviewed the efficacy of liraglutide once daily in achieving clinical guidelines-recommended glycated hemoglobin A1c levels in patients with T2D

compared with exenatide twice daily, or sitagliptin once daily, based on published literature, with an aim to elucidate the preferred choice of incretin-related therapy in treating uncontrolled T2D.

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From the Department of Medicine (Alshali), Faculty of Medicine, King Abdulaziz University, and the Department of Endocrinology (Karawagh), King Abdullah Medical Complex, Jeddah, Kingdom of Saudi Arabia.

Address correspondence and reprint request to: Dr. Khalid Z. Alshali, Associate Professor, Consultant Endocrinologist, Department of Medicine, Faculty of Medicine, King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia. E-mail: kzalshal@yahoo.com

Type 2 diabetes (T2D) is a metabolic disorder characterized by an impaired incretin effect, due to reduced activity of the glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) hormones.¹⁻³ The physiologic levels of these hormones are also found to be lower in patients with T2D compared with healthy people.⁴ Endogenous GLP-1 has a profound impact on appetite suppression by slowing the gastric passage of food and prompting feelings of satiety, consequently reducing glucagon secretion and nutrition intake.^{1,3} Furthermore, GLP-1 is associated with improvements in beta-cell function in patients with T2D.⁵

The glycated hemoglobin A1c (HbA1c) level is an important indicator of an individual's glycemic status as it conveys the average blood glucose level over several months with less chance of fluctuations due to stress.^{6,7} Clinical guidelines for the management of T2D provide guidance on HbA1c target levels to be maintained in order to avoid or minimize the risk of developing long term diabetes-related morbidities. Guidelines such as the American Diabetes Association (ADA) and

the International Diabetes Federation recommend maintaining an HbA1c level <53 mmol/mol (<7%) for most non-pregnant adults with T2D, with a target of ≤48 mmol/mol (≤6.5%) for those who are not at risk of significant hypoglycemia, or other side effects.^{7,8} Regional guidelines formulated for the Middle East also recommend the target HbA1c level <53 mmol/mol (<7%) propounded by the ADA in conjunction with the European Association for the Study of Diabetes (EASD).^{9,10} The more stringent target HbA1c of ≤48 mmol/mol (≤6.5%) for T2D patients is recommended in the joint guidelines developed by the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE).^{11,12} It is important to note that achieving and maintaining such stringent glycemic targets through pharmacological interventions also carries the risk of side effects such as hypoglycemia and weight gain. Therefore, appropriate and careful selection of anti-hyperglycemic therapies, keeping in mind the requirements of individual patients, is essential to safely attain the HbA1c levels recommended by clinical guidelines.¹³ Anti-hyperglycemic therapies that can augment the natural incretin response have gained prominence for patients with T2D over the past decade.¹² These incretin-related therapies consist of incretin mimetics, or GLP-1 receptor agonists (RAs) and incretin enhancers or dipeptidyl peptidase-4 (DPP-4) inhibitors.¹² Incretin therapy lowers HbA1c, fasting plasma glucose, and postprandial plasma glucose levels and does not increase the risk of hypoglycemia, or body weight gain in patients with T2D.^{14,15}

Glucagon-like peptide-1 receptor agonists.

Endogenous GLP-1 has a half-life of less than 2 minutes due to rapid inactivation by the DPP-4 enzyme.¹⁶ Therefore, synthetic and human GLP-1 RAs were developed to be resistant to the effects of the DPP-4 enzyme, while retaining the glucoregulatory properties of human GLP-1. The guidelines of the ADA recommend using GLP-1 RAs as a secondary pharmacological agent to be added to the first-line therapy and those of the AACE/ACE recommend using GLP-1 RAs over DPP-4 inhibitors, as monotherapy in case of metformin failure, or as dual or triple therapy.^{11,13}

Exenatide is a synthetic GLP-1 RA with 53% homology to human GLP-1 and a half-life of 2.4 hours.¹⁷

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It was the first incretin-related pharmacological agent to receive United States Food and Drug Administration (US FDA) approval in 2005 for use in treating patients with T2D.¹⁷ Concentrations of exenatide can be detected up to 10 hours after dosing and it can be administered twice daily (bid).¹⁷

Liraglutide is the first human GLP-1 RA and was approved by the US FDA in 2010 for use as an adjunct to diet and exercise to improve glycemic control in adults with T2D.¹⁸ The liraglutide molecule is capable of reversibly binding to albumin due to its structural modifications compared with native GLP-1, resulting in slower absorption.^{18,19} Liraglutide has 97% homology to native GLP-1, a half-life of up to 13 hours, and can be administered once daily (qd).^{18,19}

Improved HbA1c levels in comparison to other oral antidiabetic drugs (OADs), or placebo have been reported in patients with T2D who have received therapy with either liraglutide qd or exenatide bid with or without other anti-hyperglycemic therapies.²⁰⁻²² In the 52-week Liraglutide Effect and Action in Diabetes (LEAD-3) study of 746 patients with T2D, monotherapy with liraglutide 1.2 and 1.8 mg qd decreased HbA1c levels by 9 mmol/mol (0.8%) and 12 mmol/mol (1.1%), from a baseline HbA1c level of 65 mmol/mol (8.1%) compared with glimepiride 8 mg qd (-5 mmol/mol [-0.5%]).²⁰ In a study conducted by Seino et al,²¹ more patients attained the target HbA1c of <53 mmol/mol (<7%) with liraglutide compared with glyburide (49% versus 30.8%; $p < 0.0001$). In a 24-week, randomized, controlled trial of 232 drug-naive patients unable to achieve glucose control with diet and exercise, Moretto et al²² reported that compared with placebo (-2 mmol/mol [-0.2%]), exenatide reduced HbA1c levels by 8 mmol/mol (0.7%) and 10 mmol/mol (0.9%) using 5 and 10 µg bid, respectively, from a baseline HbA1c level of 62 mmol/mol (7.8%). A total of 58% of patients receiving exenatide bid achieved the target HbA1c of <53 mmol/mol (<7%) compared with placebo (19%).²² Other available GLP-1 RAs include an extended-release formulation of exenatide that can be dosed once weekly, the once-weekly GLP-1 RAs albiglutide and dulaglutide, and the short-acting GLP-1 RA lixisenatide.²³⁻²⁶

Dipeptidyl peptidase-4 inhibitors. Dipeptidyl peptidase-4 inhibitors work by inhibiting the degradation of endogenous GIP and GLP-1 by the DPP-4 enzyme.^{2,27} Sitagliptin was the first oral DPP-4 inhibitor approved by the US FDA for treating T2D in 2006²⁸ and can be administered at a dose of up to 100 mg qd. Clinical trials have demonstrated reductions of -7 to -9 mmol/mol (-0.6 to -0.8%) in mean HbA1c

levels with sitagliptin.^{29,30} Other available DPP-4 inhibitors for use in treating T2D include saxagliptin, linagliptin, vildagliptin, and alogliptin.³¹⁻³⁴

The synthetic GLP-1 RA exenatide bid, the human GLP-1 RA liraglutide qd, and the DPP-4 inhibitor sitagliptin qd are the first agents in their respective classes to be approved for the treatment of T2D and their efficacy and safety has been studied extensively in clinical trials.^{17,18,28} This article aimed to review the glycemic efficacy of liraglutide qd in achieving target HbA_{1c} levels as recommended by clinical guidelines for the treatment of T2D compared with sitagliptin qd and exenatide bid based on the published results of head-to-head studies.

Search strategy. An initial PubMed search was conducted in May 2014 for head-to-head randomized controlled trials, and observational studies published in English that compared the glycemic efficacy (HbA_{1c} reduction and proportion of patients attaining target HbA_{1c} levels) of liraglutide qd with exenatide bid and sitagliptin qd in adults with T2D. The following search terms were used: liraglutide, Victoza, sitagliptin, Januvia, exenatide, Byetta, GLP-1 receptor agonist, DPP-4 inhibitors, incretin, HbA_{1c}, glycemic efficacy, and blood glucose. Additional studies were identified from the citation sections of recovered articles and prescribing information documents of the approved medications were obtained from regulatory websites. Literature searches were again performed between May 2015 and June 2016 to update the references and to include the current prescribing information and the latest clinical guidelines.

Achieving target glycated hemoglobin A_{1c}. Liraglutide versus exenatide in head-to-head clinical

trials. In a head-to-head comparison of liraglutide and exenatide, Buse et al³⁵ conducted a 26-week, randomized, open-label, active comparator, parallel-group, multinational trial (LEAD-6) in adult T2D patients with baseline HbA_{1c} values between 53 and 97 mmol/mol (7% and 11%). Patients were randomly assigned (1:1) to liraglutide 1.8 mg qd (n=233) or exenatide 10 µg bid (n=231), both injected subcutaneously. Background therapy of metformin and/or sulfonylurea was permitted.³⁵ After 26 weeks, liraglutide significantly reduced the mean baseline HbA_{1c} value to a greater extent than exenatide bid (-12 mmol/mol versus -9 mmol/mol [-1.1% versus -0.8%], $p<0.0001$) (Table 1).³⁵ Also, the proportion of patients achieving the HbA_{1c} target of <53 mmol/mol (<7%) was significantly higher in the liraglutide group than in the exenatide group (54% versus 43%, $p=0.0015$). The proportion of patients achieving the stricter HbA_{1c} target of ≤48 mmol/mol (≤6.5%) was also significantly higher in the liraglutide group than in the exenatide group (35% versus 21%, $p<0.0001$).³⁵

In a 14-week extension of the LEAD-6 trial, patients who switched from exenatide 10 µg bid to liraglutide 1.8 mg qd experienced further improvements in the mean HbA_{1c} by 3 mmol/mol (-0.3%).³⁶ Following the switch to liraglutide, the proportion of patients achieving target HbA_{1c} levels also rose from 45.2% to 57.9% for HbA_{1c} <53 mmol/mol (<7%) and from 23.7% to 41% for HbA_{1c} ≤48 mmol/mol (≤6.5%).³⁶

Liraglutide versus sitagliptin in head-to-head clinical trials. Pratley et al³⁷ conducted a multinational, randomized, parallel-group, open-label, active-comparator trial (LIRA-DPP-4) where T2D patients previously treated with metformin monotherapy

Table 1 - Overview of clinical trials comparing liraglutide qd with exenatide bid or sitagliptin qd.

Study reference	Study design	Background therapy	Treatment groups	Mean baseline HbA _{1c} , mmol/mol (%)	HbA _{1c} change from baseline, mmol/mol (%)	Proportion of patients achieving HbA _{1c} <53 mmol/mol (<7.0%)	Proportion of patients achieving HbA _{1c} ≤48 mmol/mol (≤6.5%)
Buse et al ³⁵	Randomized, open-label, parallel-group, 26-week trial	Metformin ± sulfonylurea	Liraglutide 1.8 mg qd (n=233)	66 (8.2)	-12 (-1.1)*	54%†	35%*
			Exenatide 10 µg bid (n=231)	65 (8.1)	-9 (-0.8)	43%	21%
Pratley et al ³⁸	Randomized, open-label, parallel-group, 52-week trial	Metformin	Liraglutide 1.2 mg qd (n=225)	68 (8.4)	-14 (-1.3)*	50.3%*	24.3%‡
			Liraglutide 1.8 mg qd (n=221)	68 (8.4)	-16 (-1.5)*	63.3%*	40.4%*
			Sitagliptin 100 mg qd (n=219)	69 (8.5)	-10 (-0.9)	27.1%	16.8%

bid - twice daily, HbA_{1c} - glycated hemoglobin A_{1c}, qd - once daily. * $p<0.0001$ versus active comparator.

† $p=0.0015$ versus active comparator, ‡ p -value not significant versus active comparator.

(≥ 1500 mg qd) for at least 3 months, but with HbA1c between 58 mmol/mol and 86 mmol/mol (7.5 and 10%) were randomized (1:1:1) to either subcutaneously injected liraglutide 1.2 mg qd ($n=225$) or liraglutide 1.8 mg qd ($n=221$) or oral sitagliptin 100 mg qd ($n=219$) for 52 weeks, while continuing on existing metformin therapy.^{37,38} Baseline HbA1c levels were 68 to 69 mmol/mol (8.4 to 8.5%). The mean HbA1c reduction was significantly greater with liraglutide 1.2 mg (14 mmol/mol [-1.3%]) and liraglutide 1.8 mg (16 mmol/mol [-1.5%]) compared with sitagliptin (10 mmol/mol [-0.9%]) after 52 weeks ($p < 0.0001$).^{37,38} More patients attained the target HbA1c levels of < 53 mmol/mol ($< 7\%$) and ≤ 48 mmol/mol ($\leq 6.5\%$) with liraglutide 1.8 mg and 1.2 mg compared with those on sitagliptin after 52 weeks (Table 1).^{37,38}

Pratley et al³⁹ also conducted an exploratory investigation in which patients were switched from sitagliptin to liraglutide after 52 weeks in a 26-week extension to the LIRA-DPP-4 study. Although 52 weeks of treatment with sitagliptin resulted in a mean change of -10 mmol/mol (-0.9%) from baseline HbA1c, switching to liraglutide (1.2 or 1.8 mg qd) for the next 26 weeks was associated with further improvements in HbA1c by 2 mmol/mol (-0.2%) with liraglutide 1.2 mg qd ($p=0.006$) and 5 mmol/mol (-0.5%) with liraglutide 1.8 mg qd ($p < 0.0001$) from the 52-week values.³⁹ Also, the proportion of patients achieving the target HbA1c of < 53 mmol/mol ($< 7\%$) increased significantly from -30% to -50% after switching from sitagliptin to liraglutide for both groups ($p=0.0005$ for liraglutide 1.2 mg qd, $p=0.0026$ for 1.8 mg qd).³⁹

Results from post hoc analyses and retrospective cohort analyses. King et al⁴⁰ conducted a post hoc analysis of data from the LEAD-6 and LIRA-DPP-4 studies in T2D patients with baseline HbA1c < 64 mmol/mol ($< 8\%$). More patients achieved the HbA1c targets of < 53 mmol/mol ($< 7\%$) and ≤ 48 mmol/mol ($\leq 6.5\%$) with liraglutide 1.8 mg qd versus exenatide bid or sitagliptin qd. The difference was statistically significant in achieving target HbA1c ≤ 48 mmol/mol ($\leq 6.5\%$) (LEAD-6: 65% patients on liraglutide versus 35% patients on exenatide, $p=0.01$; LIRA-DPP-4: 53% patients on liraglutide versus 19% patients on sitagliptin, $p=0.0002$).⁴⁰ Significantly, more patients achieved target HbA1c < 53 mmol/mol ($< 7\%$) with no weight gain, or hypoglycemia with liraglutide qd compared with exenatide bid (78% versus 42%, $p=0.0023$), or sitagliptin qd (61% versus 21%, $p < 0.0001$).⁴⁰

Lee et al⁴¹ performed a retrospective cohort analysis to compare the real-world clinical effectiveness of liraglutide qd, exenatide bid and sitagliptin qd (including

sitagliptin with metformin) in the US. Data from T2D patients with at least one prescription for liraglutide qd ($n=234$), exenatide bid ($n=182$), or sitagliptin qd ($n=1757$) in 2010 and who continued treatment for at least 6 months were included in the analysis. The mean HbA1c values were similar between the 3 groups at baseline (liraglutide 62 mmol/mol [7.8%], sitagliptin 63 mmol/mol [7.9%], and exenatide 62 mmol/mol [7.8%]).⁴¹ The predicted mean change in HbA1c from baseline was significantly greater for patients on liraglutide qd (mean change of -12 mmol/mol [-1.1%]) compared with sitagliptin qd (-8 mmol/mol [-0.7%]) and exenatide bid treatment (-8 mmol/mol [-0.75%]) ($p < 0.001$). Achievement of the target HbA1c goal of < 53 mmol/mol ($< 7\%$) based on multivariate model analysis was significantly higher with liraglutide qd compared with both exenatide bid (64.4% versus 53.6% of patients, $p < 0.0001$) and sitagliptin qd (64.4% versus 49.4% of patients, $p < 0.0001$).⁴¹

Li et al⁴² performed a retrospective cohort analysis comparing clinical and economic outcomes of liraglutide and sitagliptin in patients with T2D using data from a US claims database. The mean baseline HbA1c was 63 mmol/mol (7.9%) in the liraglutide group ($n=376$) and 66 mmol/mol (8.2%) in the sitagliptin group ($n=1089$). Multivariable regression analysis performed after adjusting for differences in baseline characteristics showed that patients in the liraglutide group experienced greater reductions in HbA1c after 6 months compared with the sitagliptin group (10 mmol/mol [0.95%-points] versus 7 mmol/mol [0.6%-points]; $p < 0.01$) and were more likely to reach the HbA1c targets of < 53 mmol/mol ($< 7\%$) (52% versus 44% of patients; odds ratio 1.55, $p < 0.01$) and ≤ 48 mmol/mol ($\leq 6.5\%$) (37% versus 26%, odds ratio 2.0, $p < 0.01$).⁴²

Discussion. Uncontrolled T2D can pose grave risks of microvascular and macrovascular complications.⁷ Successful treatment of T2D requires careful and timely selection of therapies and optimization of treatment regimens to control glycemic levels, while avoiding negative consequences such as hypoglycemia and weight gain.^{10,11} Therapies that modulate glycemic control by acting on the incretin system, such as GLP-1 RAs and DPP-4 inhibitors, have become important treatment options in recent years for patients with T2D. Recent updates to several guidelines advocate the use of incretin-based therapies in second-line T2D treatment strategies based on clinical results of improved glycemic control with little or no risk of hypoglycemia or weight gain.^{10,11} However, the choice of such therapy (whether a DPP-4 inhibitor or a GLP-1 RA) usually depends

on individual requirement and recommendations by a physician.^{43,44}

Among available GLP-1 RAs, the once-weekly GLP-1 RA, exenatide extended release (ER) (Bydureon™, Wilmington, DE, USA), can offer the advantage of a single dose administration in a week compared with the once daily and twice daily dosing pattern required by liraglutide and short-acting exenatide.^{45,46} However, a comparison of this once weekly exenatide ER formulation with liraglutide by Buse et al⁴⁷ showed that patients in the liraglutide arm experienced greater glycemic control and weight reduction compared with exenatide ER, while gastrointestinal adverse events (AEs) were higher with liraglutide treatment. There is a lack of clinical experience on the use of the 3 newer GLP-1 RAs, lixisenatide bid, albiglutide once weekly and dulaglutide once weekly, in T2DM patients, and additional studies are required for greater understanding of the efficacy and safety of these agents in routine clinical practice.^{45,46} Currently, 5 DPP-4 inhibitors are available for use, including sitagliptin, saxagliptin, linagliptin, and alogliptin (all of which can be administered qd) and vildagliptin bid, of which only the first 3 are approved by the US FDA.⁴⁸ The DPP-4 inhibitors have the advantages of oral administration and better gastrointestinal tolerance, but are less effective in glycemic control, do not cause weight loss, and the use of some agents in this class could be associated with severe joint pain.^{43,44,49} On the other hand, therapy with GLP-1 RAs offers greater improvements in glycemic profile along with the additional non-glycemic benefit of weight loss, but most agents in this class need to be injected subcutaneously, are associated with gastrointestinal AEs particularly during the initial weeks of therapy, should also be evaluated for the risk of pancreatitis, and can be comparatively expensive.^{43,44}

Liraglutide, exenatide, and sitagliptin are 3 of the leading incretin-based therapies currently available for the treatment of T2D and all of these interventions allow T2D treatment intensification through mechanisms associated with a low rate of hypoglycemia and weight-limiting effect.⁵⁰ This review provides an overview of the glycemic efficacy of liraglutide qd in achieving HbA1c target levels compared with exenatide bid, or sitagliptin qd in head-to-head comparisons.

Both in randomized clinical trials and in retrospective cohort analyses, more patients achieved the target HbA1c goals of <53 mmol/mol (<7%), or ≤48 mmol/mol (≤6.5%) with liraglutide qd treatment compared with exenatide bid, or sitagliptin qd by the study end.³⁵⁻⁴² The results of the LEAD-6 study showed that liraglutide was associated with superior

overall glycemic control compared with exenatide bid.³⁵ Treatment with liraglutide 1.8 mg qd (with metformin and/or sulfonylurea) reduced HbA1c values by 12 mmol/mol (1.1%) in the LEAD-6 study, which was similar to the reduction reported in the LEAD-3 study where liraglutide 1.8 mg qd was administered as monotherapy.^{20,35} Treatment with exenatide 10 µg bid reduced HbA1c values by 9 mmol/mol (0.8%) in the LEAD-6 study, which is consistent with the reductions of 9 to 10 mmol/mol (0.8 to 0.9%) reported in other studies with exenatide.⁵¹⁻⁵³ Switching from exenatide bid to liraglutide qd resulted in further improvements in the mean HbA1c level and more than 55% of patients attained HbA1c levels <53 mmol/mol (<7%).³⁶ In the LEAD-6 study, the risk of minor hypoglycemia was lower with liraglutide 1.8 mg qd therapy compared with exenatide bid ($p=0.0131$), with similar reductions in body weight in both groups ($p=0.2235$).³⁵ Moreover, significant improvements in beta-cell function ($p<0.0001$) and fasting insulin level ($p=0.0355$) were noted with liraglutide compared with exenatide bid therapy.³⁵ While both liraglutide and exenatide have been shown to be effective at lowering HbA1c levels when administered in combination with various OADs, including metformin,⁵¹⁻⁵⁸ the current review of clinical comparisons revealed liraglutide 1.8 mg qd to be more effective in achieving HbA1c targets in T2D patients than exenatide bid.

The results of the LIRA-DPP-4 study (main trial and extension) showed that treatment with liraglutide 1.2 mg qd and 1.8 mg qd resulted in sustained and greater reductions in HbA1c and improved glycemic control to a greater extent compared with sitagliptin 100 mg qd, irrespective of the baseline HbA1c values.³⁷⁻³⁹ The incidences of hypoglycemia and adverse events were generally comparable between the liraglutide and sitagliptin groups, while body weight reduction was higher with both liraglutide groups compared with the sitagliptin group ($p<0.0001$).³⁸ Furthermore, significant improvements in beta-cell function with both liraglutide groups versus the sitagliptin group ($p<0.001$) and reduction in insulin resistance with liraglutide 1.8 mg versus sitagliptin were noted ($p=0.04$).³⁸

Results from the post hoc analysis of the LEAD-6 and LIRA-DPP-4 studies and the findings from the retrospective cohort analyses provide further supportive data regarding the greater improvements in HbA1c with liraglutide qd therapy in T2D patients compared with exenatide bid or sitagliptin qd.⁴⁰⁻⁴² A meta-analysis⁵⁹ of placebo-controlled trials with liraglutide, exenatide, sitagliptin, and vildagliptin also showed that liraglutide therapy was associated with greater reductions in HbA1c

compared with placebo than exenatide, sitagliptin, or vildagliptin therapy. The results are also in line with findings from a retrospective chart audit for patients on incretin-related therapy carried out in UK clinical practice where greater reductions in HbA1c were noted with liraglutide qd therapy after 48 weeks compared with exenatide bid and a pooled DPP-4 inhibitor group consisting of patients receiving sitagliptin, saxagliptin, and vildagliptin.⁶⁰

Baseline HbA1c is known to be a strong predictor for the potential to achieve HbA1c target levels, with a lower baseline level correlating to a higher chance of target achievement.⁶¹ In the clinical trials (LEAD-6 and LIRA-DPP-4), the baseline HbA1c levels were similar between the treatment arms.^{35,37} In the retrospective cohort analysis performed by Li et al,⁴² baseline HbA1c was slightly lower in the liraglutide arm compared with the sitagliptin arm (63 mmol/mol [7.9%] versus 66 mmol/mol [8.2%]); however, multivariate logistic regression analysis carried out after adjusting for baseline differences still demonstrated statistically significantly greater improvements in HbA1c levels with liraglutide qd ($p < 0.01$).⁴²

The marked improvements in HbA1c levels and the greater proportions of patients with T2D achieving target HbA1c levels with liraglutide qd compared with exenatide bid or sitagliptin qd are also associated with less weight gain and low risk of hypoglycemia.⁴⁰ A meta-analysis⁶¹ of 25 randomized controlled trials examining the glycemic efficacy of 3 different GLP-1 RAs (exenatide bid, exenatide once weekly, and liraglutide qd) when compared with OADs or placebo indicated that liraglutide qd and exenatide once weekly were the most effective therapies to attain HbA1c targets over exenatide bid; however, liraglutide qd was also associated with weight loss compared with exenatide once weekly. The promising results for HbA1c levels with incretin-related therapies, in general, and liraglutide qd, in particular, could have important clinical implications for regions such as the Middle East and North Africa (MENA) region that currently has over 35 million adults with diabetes.⁶² Countries in the MENA region, such as Saudi Arabia and Kuwait, have very high diabetes prevalence and multiple studies have reported inadequate glycemic control among patients with T2D from the Middle East.⁶²⁻⁶⁶ However, guidelines for T2D management from this region do not currently include newer agents such as injectable GLP-1 RAs among the recommended interventions, and there are few studies conducted to assess the safety and effectiveness of incretin-based therapies in general in the Middle East.⁶⁴ Treatment with liraglutide in a cohort of patients with

T2D from the United Arab Emirates (UAE) was shown to be well-tolerated and associated with significant reductions in HbA1c levels (up to 1.5%, $p < 0.05$), as well as improvements in body weight and systolic blood pressure across 6 months, irrespective of background therapy that included insulin as well as OADs.⁶⁷ Another study⁶⁸ conducted in a cohort of patients from the UAE on sitagliptin revealed a 0.5% decrease in mean HbA1c levels ($p \leq 0.05$) after one year, with no significant change in weight. Therapy with the DPP-4 inhibitor, vildagliptin, has shown numerically greater decreases in HbA1c versus other OADs in patients from the Middle East.⁶⁹ Further large-scale studies of incretin-related therapies are needed in this region to ascertain whether the promising results from clinical trials are carried over into the real-world of clinical practice. Studies assessing the effects of liraglutide and sitagliptin during Ramadan have shown that neither treatment exacerbates the risk of hypoglycemia during this period.⁷⁰⁻⁷²

Patients have also reported higher treatment satisfaction with liraglutide qd compared with both exenatide bid and sitagliptin qd.^{73,74} Both exenatide and liraglutide are administered by injection; however, liraglutide offers slightly better convenience and ease of dosing as it can be injected once a day while exenatide bid requires injections twice a day.⁷³ Sitagliptin, on the other hand, is administered orally; however, the greater treatment satisfaction reported with liraglutide suggests that the necessity of taking a daily injection did not outweigh the benefits seen with liraglutide therapy.⁷⁴ Cost effectiveness analyses also indicated that liraglutide qd could be cost effective in terms of improved quality-of-life and achievement of glycemic goals; however, more long-term, real-world analyses are needed in this regard.⁷⁵⁻⁷⁷

This was a general literature review examining published literature that included direct comparisons of liraglutide qd with exenatide bid, or sitagliptin qd. This review included results from randomized controlled trials as well as real-world data from large cohort studies that featured head-to-head comparisons of liraglutide qd, exenatide bid, and sitagliptin qd use in the T2D patient population. However, the randomized clinical trials included were open-label in design and did not include a placebo arm, which could have provided a useful comparison for safety parameters. Nevertheless, all 3 therapies under consideration in this review are leading drugs in their respective classes (GLP-1 RAs and DPP-4 inhibitors) with well-established safety and effectiveness from numerous clinical studies.

In conclusion, liraglutide qd therapy was associated with greater improvements in HbA1c levels and a higher proportion of patients with T2D attained HbA1c <53 mmol/mol (<7%) and ≤48 mmol/mol (≤6.5%) with comparable safety and tolerability in direct comparisons versus both exenatide bid and sitagliptin qd. Liraglutide qd therapy is also associated with significant improvements in beta-cell function and sensitivity to insulin compared with exenatide bid and sitagliptin qd, which could have important connotations in addressing the underlying physiopathologies of T2D. While comparing results from different clinical trials could be affected by differences in study design and study population, a review of direct comparisons from head-to-head trials of liraglutide qd versus exenatide bid or sitagliptin qd could potentially minimize this limitation. With spiralling rates of T2D prevalence in many countries worldwide, it is important for clinicians to consider all available therapeutic options to attain important glycemic targets such as HbA1c levels, while also focusing on patient safety by selecting glucose-lowering therapies associated with low rates of hypoglycemia. The findings from this review suggest that liraglutide qd should be considered as the first choice of incretin-related therapy over exenatide bid or sitagliptin qd for T2D patients with uncontrolled HbA1c levels.

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