Review Article

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,* MBBCh, 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 يخفض من خطر نوبات نقص الغلوكوز في الدم. كان كل من ناهض مستقبلات البتتيد الأول الشبيه بالغلوكاجون الصناعي سيتاجليبتين المسمى إكسيناتيد، وناهض مستقبلات البتتيد الأول الشبيه بالغلوكاجون البشري المسمى ليراغلوتيد، 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 ليراغلوتيد مرة يوميًا في تحقيق المستويات التي توصي بها الإرشادات للهيموجلوبين السكري في مرضى النوع الثاني من داء السكري، وذلك بالمقارنة بعقار إكسيناتيد مرتين يوميًا أو سيتاغليبتين مرة يوميًا، بناءً على المواد المنشورة، وذلك بهدف تسويغ 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.

Saudi Med J 2016; Vol. 37 (8): 834-842
doi: 10.15537/smj.2016.8.15800

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] 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 al[22] 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 2006[28] 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

Disclosure. Authors have no conflict of interests. The preparation of this manuscript was funded by Novo Nordisk Gulf, Riyadh, Saudi Arabia.

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 HbA1c 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 (HbA1c reduction and proportion of patients attaining target HbA1c 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, HbA1c, 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 A1c. Liraglutide versus exenatide in head-to-head clinical trials. In a head-to-head comparison of liraglutide and exenatide, Buse et al[35] conducted a 26-week, randomized, open-label, active comparator, parallel-group, multinational trial (LEAD-6) in adult T2D patients with baseline HbA1c 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 HbA1c 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 HbA1c 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 HbA1c 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 HbA1c by 3 mmol/mol (-0.3%).[36] Following the switch to liraglutide, the proportion of patients achieving target HbA1c levels also rose from 45.2% to 57.9% for HbA1c <53 mmol/mol (<7%) and from 23.7% to 41% for HbA1c ≤48 mmol/mol (≤6.5%).[36]

Liraglutide versus sitagliptin in head-to-head clinical trials. Pratley et al[37] 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 (≤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 al[39] 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 al[40] 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 (≤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 (≤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 al[41] 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 al[42] 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 (≤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 al[47] 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-analysis[59] 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%] vesus 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-analysis[61] 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 study[68] conducted in a cohort of patients from the UAE on sitagliptin revealed a 0.5% decrease in mean HbA1c levels ($p\leq0.05$) 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.

Acknowledgment. *The authors would like to thank Cognizant Technology Solutions for medical writing assistance funded by Novo Nordisk Gulf, Riyadh, Saudi Arabia.*

References

1. Holst JJ, Vilsbøll T, Deacon CF. The incretin system and its role in type 2 diabetes mellitus. ***Mol Cell Endocrinol*** 2009; 297: 127-136.
2. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. ***Lancet*** 2006; 368: 1696-1705.
3. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. ***Gastroenterology*** 2007; 132: 2131-2157.
4. Nauck M, Stöckmann F, Ebert R, Creutzfeldt W. Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. ***Diabetologia*** 1986; 29: 46-52.
5. Zander M, Madsbad S, Madsen JL, Holst JJ. Effect of 6-week course of glucagon-like peptide 1 on glycaemic control, insulin sensitivity, and beta-cell function in type 2 diabetes: a parallel-group study. ***Lancet*** 2002; 359: 824-830.
6. American Diabetes Association. Classification and diagnosis of diabetes. Sec. 2. In: Standards of Medical Care in Diabetes-2016. ***Diabetes Care*** 2016; 39 Suppl 1: S13-S22.
7. American Diabetes Association. Glycemic targets. Sec. 5. In Standards of Medical Care in Diabetes-2016. ***Diabetes Care*** 2016; 39 Suppl 1: S33-S40.
8. International Diabetes Federation Guideline Development Group. Global guideline for type 2 diabetes. ***Diabetes Res Clin Pract*** 2014; 104: 1-52.
9. Al-Arouj M, Al-Magd MA, Bougerra R, Buse JB, Edelman SV, Fahmy M, et al. Recommendations for management of hyperglycaemia in Arab countries. Based on the consensus statement form the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). ***Clin Diabetes (Middle East Edition)*** 2007; 6: 118-124.
10. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. ***Diabetes Care*** 2015; 38: 140-149.
11. Handelsman Y, Bloomgarden ZT, Grunberger G, Umpierrez G, Zimmerman RS, Bailey TS, et al. American Association of Clinical Endocrinologists and American College Of Endocrinology-Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan-2015. ***Endocr Pract*** 2015; 21 Suppl 1: 1-87.
12. Rodbard HW, Jellinger PS, Davidson JA, Einhorn D, Garber AJ, Grunberger G, et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycaemic control. ***Endocr Pract*** 2009; 15: 768-770.
13. American Diabetes Association. Approaches to glycemic treatment. In Standards of Medical Care in Diabetes-2016. ***Diabetes Care*** 2016; 39 Suppl 1: S52-S59.
14. Nisal K, Kela R, Khunti K, Davies MJ. Comparison of efficacy between incretin-based therapies for type 2 diabetes mellitus. ***BMC Med*** 2012; 10: 152.
15. Nauck M. Incretin therapies: highlighting common features and differences in the modes of action of glucagon-like peptide 1 receptor agonists and dipeptidyl peptidase-4 inhibitors. ***Diabetes Obes Metab*** 2016; 18: 203-216.
16. Pratley RE, Gilbert M. Degradation of glucose-dependent insulinotropic polypeptide and truncated glucagon-like peptide 1 in vitro and in vivo by dipeptidyl peptidase IV. ***Rev Diabet Stud*** 2008; 5: 73-94.
17. Byetta® (exenatide bid) [package insert]. AstraZeneca Pharmaceuticals LP. [Updated 2014. Accessed 2015 March 19]. Available from URL: http://www.azpicentral.com/byetta/pi_byetta.pdf
18. Victoza® (liraglutide qd). European Medical Agency. Summary of Product Characteristics. Novo Nordisk A/S. [Updated 2014. Accessed 2015 March 19]. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001026/WC500050017.pdf
19. Chia CW, Egan JM. Incretin-based therapies in type 2 diabetes mellitus. ***J Clin Endocrinol Metab*** 2008; 93: 3703-3716.
20. Garber A, Henry R, Ratner R, Garcia-Hernandez PA, Rodriguez-Pattzi H, Olvera-Alvarez I, et al. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomized, 52-week, phase III, double-blind, parallel-treatment trial. ***Lancet*** 2009; 373: 473-481.
21. Seino Y, Rasmussen MF, Nishida T, Kaku K. Efficacy and safety of the once-daily human GLP-1 analogue, liraglutide, vs glibenclamide monotherapy in Japanese patients with type 2 diabetes. ***Curr Med Res Opin*** 2010; 26: 1013-1022.

22. Moretto TJ, Milton DR, Ridge TD, Macconell LA, Okerson T, Wolka AM, et al. Efficacy and tolerability of exenatide monotherapy over 24 weeks in antidiabetic drug-naive patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, parallel-group study. ***Clin Ther*** 2008; 30: 1448-1460.
23. Bydureon™ (exenatide extended-release for injectable suspension) [prescribing information]. AstraZeneca Pharmaceuticals LP [Updated 2015. Accessed 2016 June 03]. Available from URL: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022200s000lbl.pdf
24. Tanzeum® (albiglutide) [package insert]. GlaxoSmithKline LLC. [Updated 2014. Accessed 2016 June 03]. Available from URL: https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Tanzeum/pdf/TANZEUM-PI-MG-IFU-COMBINED.PDF
25. Trulicity® (dulaglutide) [prescribing information]. Eli Lilly and Company. [Updated 2014. Accessed 2016 June 03]. Available from URL: http://pi.lilly.com/us/trulicity-uspi.pdf
26. Lyxumia® (lixisenatide). European Medical Agency. Summary of product characteristics. [Updated 2013. Accessed 2016 June 03]. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002445/WC500140401.pdf
27. Ahrén B. DPP-4 inhibitors. ***Best Pract Res Clin Endocrinol Metab*** 2007; 21: 517-533.
28. Januvia® (sitagliptin qd) [package insert]. Merck & Co Inc. [Updated 2015. Accessed 2016 June 03]. Available from URL: http://www.merck.com/product/usa/pi_circulars/j/januvia/januvia_pi.pdf
29. Hermansen K, Kipnes M, Luo E, Fanurik D, Khatami H, Stein P, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin. ***Diabetes Obes Metab*** 2007; 9: 733-745.
30. Harashima SI, Ogura M, Tanaka D, Fukushima T, Wang Y, Koizumi T, et al. Sitagliptin add-on to low dosage sulphonylureas: efficacy and safety of combination therapy on glycemic control and insulin secretion capacity in type 2 diabetes. ***Int J Clin Pract*** 2012; 66: 465-476.
31. Onglyza® (saxagliptin) [package insert]. Bristol-Myers Squibb Company and AstraZeneca Pharmaceuticals LP. [Updated 2016. Accessed 2016 June 03]. Available from URL: http://www.azpicentral.com/onglyza/pi_onglyza.pdf
32. Tradjenta® (linagliptin) [package insert]. Boehringer Ingelheim. [Updated 2016. Accessed 2016 June 03]. Available from URL: http://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Tradjenta/Tradjenta.pdf
33. Galvus® (vildagliptin). European Medical Agency. Summary of Product Characteristics. [Updated 2016. Accessed 2016 June 03]. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000771/WC500020327.pdf
34. Nesina® (alogliptin) [package insert]. Takeda Pharmaceuticals America Inc. [Updated 2013. Accessed 2016 June 03]. Available from URL: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022271s000lbl.pdf
35. Buse JB, Rosenstock J, Sesti G, Schmidt WE, Montanya E, Brett JH, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomized, parallel-group, multinational, open-label trial (LEAD-6). ***Lancet*** 2009; 374: 39-47.
36. Buse JB, Sesti G, Schmidt WE, Montanya E, Chang CT, Xu Y, et al. Switching to once-daily liraglutide from twice-daily exenatide further improves glycemic control in patients with type 2 diabetes using oral agents. ***Diabetes Care*** 2010; 33: 1300-1303.
37. Pratley RE, Nauck M, Bailey T, Montanya E, Cuddihy R, Filetti S, et al. Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. ***Lancet*** 2010; 375: 1447-1456.
38. Pratley R, Nauck M, Bailey T, Montanya E, Cuddihy R, Filetti S, et al. One year of liraglutide treatment offers sustained and more effective glycaemic control and weight reduction compared with sitagliptin, both in combination with metformin, in patients with type 2 diabetes: a randomised, parallel-group, open-label trial. ***Int J Clin Pract*** 2011; 65: 397-407.
39. Pratley RE, Nauck MA, Bailey T, Montanya E, Filetti S, Garber AJ, et al. Efficacy and safety of switching from the DPP-4 inhibitor sitagliptin to the human GLP-1 analog liraglutide after 52 weeks in metformin-treated patients with type 2 diabetes: a randomized, open-label trial. ***Diabetes Care*** 2012; 35: 1986-1993.
40. King AB, Montanya E, Pratley RE, Blonde L, Svendsen CB, Donsmark M, et al. Liraglutide achieves A1c targets more often than sitagliptin or exenatide when added to metformin in patients with type 2 diabetes and a baseline A1c<8.0%. ***Endocr Pract*** 2013; 19: 64-72.
41. Lee WC, Dekoven M, Bouchard J, Massoudi M, Langer J. Improved real-world glycaemic outcomes with liraglutide versus other incretin-based therapies in type 2 diabetes. ***Diabetes Obes Metab*** 2014; 16: 819-826.
42. Li Q, Chitnis A, Hammer M, Langer J. Real-world clinical and economic outcomes of liraglutide versus sitagliptin in patients with type 2 diabetes mellitus in the United States. ***Diabetes Ther*** 2014; 5: 579-590.
43. Scheen AJ. Which incretin-based therapy for type 2 diabetes? ***Lancet*** 2014; 384: 1325-1327.
44. Cobble M. Differentiating among incretin-based therapies in the management of patients with type 2 diabetes mellitus. ***Diabetol Metab Syndr*** 2012; 4: 8.
45. Trujillo JM, Nuffer W, Ellis SL. GLP-1 receptor agonists: a review of head-to-head clinical studies. ***Ther Adv Endocrinol Metab*** 2015; 6: 19-28.
46. Madsbad S. Review of head-to-head comparisons of glucagon-like peptide-1 receptor agonists. ***Diabetes Obes Metab*** 2016; 18: 317-332.
47. Buse JB, Nauck M, Forst T, Sheu WH, Shenouda SK, Heilmann CR, et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. ***Lancet*** 2013; 381: 117-124.
48. Gupta V, Kalra S. Choosing a gliptin. ***Indian J Endocrinol Metab*** 2011; 15: 298-308.
49. U.S. Food and Drug Administration. FDA drug safety communication: FDA warns that DPP-4 inhibitors for type 2 diabetes may cause severe joint pain. [Updated 2015. Accessed 2016 June 03]. Available from URL: http://www.fda.gov/Drugs/DrugSafety/ucm459579.htm
50. George RE, Joseph S. A review of newer treatment approaches for type-2 diabetes: Focusing safety and efficacy of incretin based therapy. ***Saudi Pharm J*** 2014; 22: 403-410.

51. Buse JB, Henry RR, Han J, Kim DD, Fineman MS, Baron AD, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. ***Diabetes Care*** 2004; 27: 2628-2635.
52. Kendall DM, Riddle MC, Rosenstock J, Zhuang D, Kim DD, Fineman MS, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. ***Diabetes Care*** 2005; 28: 1083-1091.
53. Zinman B, Hoogwerf BJ, Durán García S, Milton DR, Giaconia JM, Kim DD, et al. The effect of adding exenatide to a thiazolidinedione in suboptimally controlled type 2 diabetes: a randomised trial. ***Ann Intern Med*** 2007; 146: 477-485.
54. Derosa G, Franzetti IG, Querci F, Carbone A, Ciccarelli L, Piccinni MN, et al. Exenatide plus metformin compared with metformin alone on ß-cell function in patients with type 2 diabetes. ***Diabet Med*** 2012; 29: 1515-1523.
55. Nauck M, Frid A, Hermansen K, Shah NS, Tankova T, Mitha IH, et al. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: The LEAD (Liraglutide Effect and Action in Diabetes)-2 study. ***Diabetes Care*** 2009; 32: 84-90.
56. Russell-Jones D, Vaag A, Schmitz O, Sethi BK, Lalic N, Antic S, et al. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. ***Diabetologia*** 2009; 52: 2046-2055.
57. Seino Y, Rasmussen MF, Nishida T, Kaku K. Glucagon-like peptide-1 analog liraglutide in combination with sulfonylurea safely improves blood glucose measures vs sulfonylurea monotherapy in Japanese patients with type 2 diabetes: Results of a 52-week, randomized, multicenter trial. ***J Diabetes Investig*** 2011; 2: 280-286.
58. Zinman B, Gerich J, Buse JB, Lewin A, Schwartz S, Raskin P, et al; LEAD-4 Study Investigators. Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). ***Diabetes Care*** 2009; 32: 1224-1230.
59. Fakhoury WK, Lereun C, Wright D. A meta-analysis of placebo-controlled clinical trials assessing the efficacy and safety of incretin-based medications in patients with type 2 diabetes. ***Pharmacology*** 2010; 86: 44-57.
60. Evans M, McEwan P, O'Shea R, George L. A retrospective, case-note survey of type 2 diabetes patients prescribed incretin-based therapies in clinical practice. ***Diabetes Ther*** 2013; 4: 27-40.
61. Esposito K, Mosca C, Brancario C, Chiodini P, Ceriello A, Giugliano D. GLP-1 receptor agonists and HBA1c target of <7% in type 2 diabetes: meta-analysis of randomized controlled trials. ***Curr Med Res Opin*** 2011; 27: 1519-1528.
62. International Diabetes Federation. IDF Diabetes, 7th ed. Brussels (Belgium): International Diabetes Federation; 2015.
63. Al-Elq AH. Current practice in the management of patients with type 2 diabetes mellitus in Saudi Arabia. ***Saudi Med J*** 2009; 30: 1551-1556.
64. Al-Maatouq M, Al-Arouj M, Assaad SH, Assaad SN, Azar ST, Hassoun AA, et al. Optimising the medical management of hyperglycaemia in type 2 diabetes in the Middle East: pivotal role of metformin. ***Int J Clin Pract*** 2010; 64: 149-159.
65. Al-Akour NA, Khader YS, Alaoui AM. Glycemic control and its determinants among patients with type 2 diabetes mellitus attending a teaching hospital. ***J Diabetes Metab*** 2011; 2:129.
66. Khattab M, Khader YS, Al-Khawaldeh A, Ajlouni K. Factors associated with poor glycemic control among patients with type 2 diabetes. ***J Diabetes Complications*** 2010; 24: 84-89.
67. Ghuman NK, Saadah LM, Al Najjar MS, Shaheen DY, Am SI, Al Ali MM. Effectiveness of liraglutide in type II diabetes mellitus management: experience in Emirati patients. ***Clin Med Insights Endocrinol Diabetes*** 2015; 8: 67-72.
68. Khalil AB, Beshyah SA, Benbarka MM, DaBell J, Bernsen R. The effect of sitagliptin therapy in suboptimally controlled metformin-treated type 2 diabetes patients: a Middle Eastern experience. ***Int J Diabetes & Metab*** 2010; 18: 55-58.
69. Saab C, Al-Saber FA, Haddad J, Jallo MK, Steitieh H, Bader G, et al. Effectiveness and tolerability of second-line treatment with vildagliptin versus other oral drugs for type 2 diabetes in a real-world setting in the Middle East: results from the EDGE study. ***Vasc Health Risk Manag*** 2015; 11: 149-155.
70. Brady EM, Davies MJ, Gray LJ, Saeed MA, Smith D, Hanif W, et al. 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.
71. Khalifa AA, El Rashid AO, Bashier AMK (2015) Safety and efficacy of liraglutide as an add-on therapy to pre-existing anti-diabetic regimens during Ramadan, A Prospective Observational Trial. ***J Diabetes Metab*** 2015; 6: 590.
72. Al Sifri S, Basiounny A, Echtay A, Al Omari M, Harman-Boehm I, Kaddaha G, et al. The incidence of hypoglycaemia in Muslim patients with type 2 diabetes treated with sitagliptin or a sulphonylurea during Ramadan: a randomised trial. ***Int J Clin Pract*** 2011; 65: 1132-1140.
73. Schmidt WE, Christiansen JS, Hammer M, Zychma MJ, Buse JB. Patient-reported outcomes are superior in patients with type 2 diabetes treated with liraglutide as compared with exenatide, when added to metformin, sulphonylurea or both: results from a randomized, open-label study. ***Diabet Med*** 2011; 28: 715-723.
74. Davies M, Pratley R, Hammer M, Thomsen AB, Cuddihy R. Liraglutide improves treatment satisfaction in people with type 2 diabetes compared with sitagliptin, each as an add on to metformin. ***Diabet Med*** 2011; 28: 333-337.
75. DeKoven M, Lee WC, Bouchard J, Massoudi M, Langer J. Real-world cost-effectiveness: lower cost of treating patients to glycemic goal with liraglutide versus exenatide. ***Adv Ther*** 2014; 31: 202-216.
76. Valentine WJ, Palmer AJ, Lammert M, Langer J, Brändle M. Evaluating the long-term cost-effectiveness of liraglutide versus exenatide BID in patients with type 2 diabetes who fail to improve with oral antidiabetic agents. ***Clin Ther*** 2011; 33: 1698-1712.
77. Lee WC, Samyshkin Y, Langer J, Palmer JL. Long-term clinical and economic outcomes associated with liraglutide versus sitagliptin therapy when added to metformin in the treatment of type 2 diabetes: a CORE Diabetes Model analysis. ***J Med Econ*** 2012; 15 Suppl 2: 28-37.