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The Role of Glucagon-Like Peptide-1 Receptor Agonists in Type 2 Diabetes: Understanding How Data Can Inform Clinical Practice in Korea

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Glucagon-like peptide-1 receptor agonists (GLP-1RAs) reduce glycosylated hemoglobin (HbA1c, 0.5% to 1.0%), and are associated with moderate weight loss and a relatively low risk of hypoglycemia. There are differences between Asian and non-Asian populations. We reviewed available data on GLP-1RAs, focusing on Korean patients, to better understand their risk/benefit profile and help inform local clinical practice. Control of postprandial hyperglycemia is important in Asians in whom the prevalence of post-challenge hyperglycemia is higher (vs. non-Asians). The weight lowering effects of GLP-1RAs are becoming more salient as the prevalence of overweight and obesity among Korean patients increases. The higher rate of gastrointestinal adverse events amongst Asian patients in clinical trials may be caused by higher drug exposure due to the lower body mass index of the participants (vs. non-Asian studies). Data on the durability of weight loss, clinically important health outcomes, safety and optimal dosing in Korean patients are lacking. Use of GLP-1RAs is appropriate in several patient groups, including patients whose HbA1c is uncontrolled, especially if this is due to postprandial glucose excursions and patients who are overweight or obese due to dietary problems (e.g., appetite control). The potential for gastrointestinal adverse events should be explained to patients at treatment initiation to facilitate the promotion of better compliance.

Keywords: Clinical management; Diabetes mellitus, type 2; Glucagon-like peptide-1 receptor agonists; Glycemic control; Hyperglycemia; Postprandial period

INTRODUCTION

Type 2 diabetes mellitus (T2DM) has become a worldwide epidemic. It is estimated that 60% of the world's diabetic population is in Asia [1]. This rapid increase in the prevalence of T2DM in Asia has been fuelled by urbanization, economic growth and associated changes in diet and physical activity levels [2]. Specifically, in Korea, data derived from the Korean National Health and Nutrition Examination Survey shows that T2DM prevalence has increased moderately over the last decade from 7.7%

in 2001 [3] to 10.2% in 2010 [4]. The most recent data report that the overall prevalence of diabetes in adults aged 30 years or older is 12.4% [5].

In general, Asian populations tend to develop diabetes at a younger age and at lower body mass index (BMI) levels than has been observed in Caucasian populations [1]. Recent research in Korea has, however, revealed differences between both gender and age groups: prevalence had decreased amongst women aged 30 to 59 years (6.9% in 2001 to 4.5% in 2010), but increased amongst males aged 60 years or more (15.9% in 2001 to 21.6%

in 2010) [4]. A similar age-related trend is also reflected in data from the Korean Health Insurance Review and Assessment database, in which there were significant ($P<0.001$) decreases in annual incidence rates in younger adults (20 to 49 years) and increases in the elderly (70 to 79 years) [6].

In recognition of the progressive nature of T2DM, the current Korean Clinical Practice Guidelines (Korean Diabetes Association) suggest a stepped interventional approach. Excessive calorie intake, poor dietary quality and sedentary lifestyle all increase diabetes risk [2]. Lifestyle modification (which incorporates diet, exercise, and education) remains the foundation of the current clinical guidelines. However, because lifestyle modification alone does not enable glycemic goals to be achieved or maintained in most patients, metformin monotherapy should be added at, or soon after, diagnosis, unless there are contraindications or intolerance. Ultimately the addition of a basal insulin either alone or in combination with other agents will be required to maintain glucose control [7]. Glycosylated hemoglobin (HbA1c) plays an important role in monitoring and targeting glycemic control and is the gold standard index for follow-up of glycemic control. After lifestyle modification, treatment options are stratified according to the individual's HbA1c status; patients whose HbA1c is <8% would initially receive oral hypoglycemic agents only, those in whom it is 8% to 10% would receive oral hypoglycemic agent combination therapy with basal insulin and those whose HbA1c is >10% would receive insulin with or without oral hypoglycemic agents. Patients not at target (ideally ≤6.5%) within 2 to 6 months would receive an additional oral hypoglycemic agent (e.g., triple therapy) or a multiple-component insulin regimen again with or without oral hypoglycemic agents.

Within these guidelines glucagon-like peptide-1 receptor agonists (GLP-1RAs) are recognized as providing a moderate (0.5% to 1.0%) reduction in HbA1c, with no hypoglycemia and no weight gain. However, there are some concerns with respect to gastrointestinal (GI) side effects and the lack of long-term established safety profile [7]. In this paper we review recent data on GLP-1RAs to help better understand their current risk/benefit profile and provide primary care practitioners with guidance on how this evidence can inform their clinical practice.

GLP-1RAs: GLOBAL EXPERIENCE

GLP-1 is an incretin hormone secreted from GI L-cells early (within 10 minutes) after an ingested meal [8,9]. GLP-1 stimulates insulin secretion in a glucose-dependent manner, suppresses glucagon secretion, delays gastric emptying, and suppresses appetite. This combination of effects makes a significant contribution to glucose homeostasis, particularly the control of postprandial glucose.

The incretin response is markedly attenuated in people with T2DM [10], making the incretin based system an attractive therapeutic target. However, the short plasma half-life (1 to 2 minutes) of GLP-1 limits its suitability as a therapeutic agent for diabetes. Incretin enhancers, including dipeptidyl-peptidase 4 (DPP4) inhibitors and GLP-1RAs have therefore emerged as a novel class of glucose-lowering therapy. A systematic review aimed at evaluating the comparative effectiveness of these two drug classes has found both to be effective, with HbA1c reductions of 0.59% to 0.90% with DPP4 inhibitors and 0.77% to 1.62% with GLP-1RAs [11]. Here we focus only on the GLP-1RAs, which mimic the effects of endogenous GLP-1, thereby stimulating pancreatic insulin secretion in a glucose dependent fashion, supressing glucagon out-put, slowing gastric emptying and decreasing appetite.

Overall, the clinical advantages of GLP-1RAs are established in the literature; they provide significant improvements in glycemic control with a relatively low risk of hypoglycemia and are associated with moderate, but significant, weight loss (up to 3 kg in some clinical trials). Efficacy has been confirmed in a meta-analysis of 17 randomized trials comparing GLP-1RAs (exenatide, liraglutide, albiglutide, taspoglutide, lixisenatide) with placebo or an active comparator (insulin glargine, DPP4 inhibitor, thiazolidinedione, sulfonylurea) in patients with T2DM and suboptimal control on one or two oral hypoglycemic agents (metformin and/or sulfonylurea). Although the duration of the individual trials ranged from 8 to 30 weeks, overall, in comparison to placebo, all GLP-1RAs reduced HbA1c by approximately 1% (treatment difference 0.47% to 1.56%) [12].

Body weight reduction with GLP-1RAs has been confirmed in a meta-analysis of 21 industry-sponsored trials comparing GLP-1RAs with placebo, no intervention, or other diabetes medications in overweight patients with or without diabetes (weighted mean difference, –2.9 kg; 95% confidence interval [CI], –3.6 to –2.2). The mean weight reduction in patients with diabetes (18 trials) was –2.8 [13]. However, long-terms data on the durability of this effect are currently lacking.

In addition, GLP-1RAs have beneficial effects on cardiovascular (CV) risk factors (body weight, blood pressure, postprandial lipids, markers of oxidative stress) [14,15] with no sugges-

tion of increased risk of CV disease: for example, exenatide CV disease-extended events, relative risk (RR) 0.69 (95% CI, 0.46 to 1.04) [16]; liraglutide major adverse CV events, incidence ratio 0.73 (95% CI, 0.38 to 1.41) [17]. In a recent ultrasonography study, 3 months treatment with a GLP-1RA induced a redistribution of adipose tissue deposits, which may contribute to a better CV risk profile in patients with T2DM [18]. There are no long-term data to assess durability of weight loss, clinically important health outcomes (CV events, mortality), or safety of GLP-1RAs. The results of the Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results (LEADER) study, formally assessing the CV safety of liraglutide, are awaited [19].

POSTPRANDIAL HYPERGLYCEMIA AND THE ATTAINMENT OF HbA1c TARGETS

The pathogenesis and management of postprandial hyperglycemia has recently been reviewed [20]. Control of postprandial hyperglycemia is an important aspect of overall glycemic control and may contribute to lower CV morbidity and mortality. Data suggest that reduction of postprandial hyperglycemia may be particularly beneficial for patients early in the progression of diabetes. The relevance of postprandial hyperglycemia is heightened as HbA1c levels decrease; thus, focusing on strategies to control it may increase a patient's ability to achieve their HbA1c target. Recognizing the importance of postprandial glucose, international organizations (American Association of Clinical Endocrinologists/American College of Endocrinology, International Diabetes federation, American Diabetes Association) now provide 2-hour postprandial glucose targets of between 7.8 to 10.00 mmol/L (140 to 180 mg/dL) in their treatment guidelines [21-23].

Data from the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Asia (DECODA) [24] and Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) [25] studies suggest that the prevalence of post-challenge hyperglycemia is higher in Asian patients than it is in Caucasians. In a study of 68 Korean patients with well-controlled T2DM, glycemic variability and total glucose exposure were both mostly explained by postprandial glucose [26]. It has been suggested that the high carbohydrate diet eaten by Asians, including Koreans, may increase postprandial glucose more rapidly than does a lower carbohydrate diet [27]. In the authors' experience, postprandial hyperglycemia continues to

present a problem when determining choice of treatment in patients with T2DM; in Korea anecdotal reports suggest that 50% to 60% of patients may be affected by postprandial glucose excursions. When lifestyle interventions have failed, the addition of oral anti diabetic agents (α glucosidase inhibitors or meglitinides) [28], a DPP4 inhibitor [29], short- or prandial-acting GLP-1RA [30], or short-acting insulin (for patients already on basal insulin) may be of benefit.

The GLP-1RA class can be subdivided into two types: short-acting agonists and long-acting agonists, which each have different mechanisms of action and result in different effects on fasting and postprandial glucose levels [14]. Short-acting GLP-1RAs (exenatide twice-daily and lixisenatide once a day) act intermittently to activate the GLP-1 receptor and slow gastric emptying exerting their effects predominantly on postprandial plasma glucose [20,31]. Phase II data and the results from randomised controlled clinical trials consistently demonstrate that these GLP-1RAs reduce postprandial plasma glucose more effectively than they do fasting plasma glucose [20,32-34]. For example, adding exenatide twice-daily to basal insulin (alone or in combination with metformin and/or pioglitazone), lead to significant reductions in morning and evening 2-hour postprandial excursions (both $P<0.001$ vs. placebo) [35] whilst lixisenatide 20 μg once a day has been shown to significantly reduce postprandial glucose when compared with placebo after breakfast ($P<0.0001$), lunch ($P<0.001$), and dinner ($P<0.05$) [35,36]. It is because of this effect on postprandial glucose that short-acting GLP-1RAs may be considered as prandial-acting GLP-1RAs [9,34,37].

In contrast long-acting GLP-1RAs (liraglutide, dulaglutide, exenatide long-acting release [LAR]) lead to sustained activation of the GLP-1 receptor and have a greater impact on fasting plasma glucose and a lesser impact on gastric emptying owing to tachyphylaxis [31]. To date there have been five studies directly comparing short- and long-acting GLP-1RAs, each demonstrating that the latter have a lesser effect on postprandial glucose. In DURATION-1, exenatide 10 μg twice-daily had a greater effect on postprandial glucose than did exenatide LAR 2 mg once weekly (least-squares mean±standard error −6.9 mmol/L vs. −5.3±0.5 mmol/L, respectively,) after 30 weeks of treatment [38]. Similar results were found in the Liraglutide Effect and Action in Diabetes (LEAD) 6 study; the estimated difference in postprandial glucose reduction was higher with exenatide 10 μg twice-daily than with liraglutide 1.8 mg once a day, when measured at breakfast (1.33 mmol/L, $P<0.0001$) and

at dinner (1.01 mmol/L, $P<0.0005$) [20,39]. In a study comparing lixisenatide 20 µg once a day and liraglutide 1.8 mg once a day in patients with T2DM insufficiently controlled on metformin, more patients in the lixisenatide group achieved a 2-hour postprandial plasma glucose of <7.8 mmol/L (69% vs. 29%) [40]. In a study comparing once-daily lixisenatide with liraglutide in patients on optimised insulin glargine with or without metformin therapy improvement in postprandial glucose levels was significantly greater with lixisenatide 20 µg once a day versus liraglutide 1.2 and 1.8 mg once a day ($P<0.0001$ for both comparisons) [41]. Most recently, the Assessment of Weekly AdministRation of LY2189265 (dulaglutide) in Diabetes-1 (AWARD-1) study, comparing dulaglutide 0.75 and 1.5 mg once weekly with exenatide 10 µg twice-daily, demonstrated significantly greater reductions in the mean of all 2-hour postprandial glucose excursions with exenatide than in the two dulaglutide dose groups ($P<0.001$ for both comparisons) [42].

KOREAN-SPECIFIC EFFICACY AND SAFETY DATA

Recently published data have demonstrated differences in the efficacy of GLP-1RAs between Asian and non-Asian populations [43]. Whilst this meta-analysis included data from studies with liraglutide and exenatide, it demonstrated a significant difference in the HbA1c-lowering efficacy of GLP-1RAs in Asians (weighted mean difference –0.32 [–0.64; 0.01]; $P=0.044$) and a trend for more Asian patients to achieve target HbA1c goals. Nevertheless, data from a population with a significant proportion of Korean patients are rare. Amongst the studies included in the recent meta-analysis three included only Japanese patients [44-46] whilst one included patients of Asian descent, of which 17% were Korean [47]. In addition to the study by Gao et al. [47], four other studies, have reported efficacy data for GLP-1RAs in Korean patients with T2DM (Table 1) [30,48-50].

Gao et al. [47] evaluated the efficacy of exenatide in Asian patients with T2DM inadequately controlled with oral agents, showing improved glycemic control (mean HbA1c reduction: –1.2% vs. –0.4%, $P<0.001$), and greater weight reduction (–1.2 kg vs. –0.1 kg) compared with placebo.

Shin et al. [49] reported the results of a retrospective cohort analysis of 52 Korean patients; 6 months' therapy with exenatide had significantly reduced HbA1c (8.5% to 6.7%, $P<0.001$) and body weight (82.3 to 78.6 kg, $P<0.001$); no serious adverse events were reported. Of note the patients were young (mean age 45.1 years) and obese (mean BMI 30.0 kg/m^2).

The study by Yang et al. [48] 2011 included Chinese, Indian, and Korean (167/929, 18%) patients; it demonstrated liraglutide to have a similar efficacy profile in Asian patients to that seen in Caucasian, African American and Hispanic populations in other global liraglutide phase III trials [48]. In the global HARMONY-7 study, five of the 162 study sites were in Korea. Patients who received liraglutide once a day had greater reductions in HbA1c than did those who received albiglutide once weekly. Of note the patients were older (mean age 55 years), had a long duration of diabetes (mean 8.4 years) and were obese (mean BMI >30.0 kg/m^2) [50].

The GetGoal-L-Asia study included 39.5% (123/311) Korean patients. Lixisenatide, 20 µg once a day, as add-on therapy in patients with T2DM insufficiently controlled on basal insulin (with or without sulfonylurea) significantly improved HbA1c vs. placebo and enabled more patients to achieve HbA1c target (<7% and <6.5%) [30]. Although there was a trend towards weight loss for lixisenatide ($P=0.0857$) in this study, the observed weight losses were small (–0.38 kg and +0.06 kg in the lixisenatide and placebo groups, respectively) possibly due to the low mean baseline BMI (25 kg/m^2) and body weight (66 kg).

Hypoglycemia

Fear of hypoglycemia is a major barrier to optimizing glycemic control in patients with T2DM. Hypoglycemic events increase the direct and indirect economic burden of diabetes and also have a negative impact on a patient's quality of life and confidence in diabetes self-management ability [51]. Preventing hypoglycemic events and the early detection of patients at high risk for hypoglycemia are important aspects of clinical care.

In the recent meta-analysis by Kim et al. [43], there was no significant difference in the RR of hypoglycemia with GLP-1RAs between Asian and non-Asian populations (2.8 vs. 1.5, respectively; $P=0.164$) [43]. In the study by Gao et al. [47] the incidence of symptomatic hypoglycemia was higher in exenatide-treated patients than those who received placebo (36% and 9%, respectively; $P<0.001$). Hypoglycemia rates (events/patient-year) for patients taking exenatide with metformin alone were 1.8 and this increased to 4.7 amongst those taking metformin plus a sulfonylurea. There were no reported incidences of hypoglycemia in the retrospective cohort analysis 52 Korean patients after 6 months' therapy with exenatide [49]. Similarly, in the study by Yang et al. [48], only two subjects in the glimepiride group reported major hypoglycemia while

Table 1. Summary of data from studies with GLP-1RAs which have included Korean patients with type 2 diabetes

Study	Design	Proportion Korean patients	GLP-1RA	Mean change in				Discontinuation due to TEAE, n (%)	Proportion of patients with			
				HbA1c from baseline, %	Bodyweight from baseline, kg	FPG level from baseline, mmol/L	Morning 2-hr PPG level from baseline, mmol/L		GI adverse events, %			Hypoglycemia, %
									Nausea	Vomiting	Diarrhea	
Gao et al. (2009) [47]	R, DB, PC, PG, MC 12 wk (n=466)	17%	Exenatide	Exenatide: -1.2 Placebo: -0.4 P<0.001	Exenatide: -1.2 Placebo: -0.1 P<0.001	Exenatide: -1.3 Placebo: -0.2 P<0.001	Postprandial glucose excursions: P<0.001	Exenatide: 18 (8) Placebo: 1 (0.4)	Exenatide: 25.2 Placebo: 0.9	Exenatide: 15.8 Placebo: Nil	Exenatide: 3.8 Placebo: 2.6	Symptomatic events: Exenatide (35.5%) Placebo: (9.1%) Major events: Exenatide (Nil) Placebo (Nil)
Yang et al. (2011) [48]	R, DB, PC, PG 16 wk (n=929)	18%	Liraglutide[a]	Liraglutide: -1.45 Glimperide: -1.39 P=NS	Liraglutide: -2.4 Glimperide: 0.1 P<0.01	Liraglutide: -2.12 Glimperide: -2.18 P=NS	Liraglutide: -3.51 Glimperide: -2.60 P<0.0001	Liraglutide: 30 (12.8) Glimperide: 3 (1.3)	No data presented	No data presented	No data presented	Minor events: No data presented Major events: Exenatide (Nil) Glimperide (2)
Seino et al. (2012) [30] GETGOAL-L-ASIA	R, DB, PC, PG, MC 24 wk (n=311)	39.5%	Lixisenatide	Lixisenatide: -0.77 Placebo: 0.11 P<0.0001	Lixisenatide: -0.38 Placebo: 0.06 P=0.08	Lixisenatide: -0.42 Placebo: 0.25 P=0.0187	Lixisenatide: -7.96 Placebo: -0.14 P<0.0001	Lixisenatide: 14 (9) Placebo: 5 (3)	Lixisenatide: 39.6 Placebo: 4.5	Lixisenatide: 18.2 Placebo: 1.9	Lixisenatide: 6.5 Placebo: 2.5	Symptomatic events: Lixisenatide (43%) Placebo (24%) Major events: Lixisenatide (Nil) Placebo (Nil)

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Table 1. Continued

Study	Design	Proportion Korean patients	GLP-1RA	Mean change in				Proportion of patients with				
				HbA1c from baseline, %	Bodyweight from baseline, kg	FPG level from baseline, mmol/L	Morning 2-hr PPG level from baseline, mmol/L	Discontinuation due to TEAE, n (%)	GI adverse events, %			Hypoglycemia, %
									Nausea	Vomiting	Diarrhea	
Shin et al. (2012) [49]	Retrospective cohort 24 wk (n=143)	100%	Exenatide	Exenatide: -1.7 P<0.001	Exenatide: -3.7 P<0.001	No data presented	No data presented	No data presented	16.1	11.9	Nil	Nil
Pratley et al. (2014) [50] HARMONY7	R, DB, PC, PG, MC 32 wk (n=812)	No data presented Korea= 5/162 study sites	Albiglutide	Albiglutide: -0.79 Liraglutide: -0.98 P=NS	Albiglutide: -0.64 Liraglutide: -2.19 P<0.001	Albiglutide: -1.22 Liraglutide: -1.68 P=0.0048	No data presented	Albiglutide: 31 (7.8) Liraglutide: 41 (10.0)	Albiglutide: 9.9 Liraglutide: 29.2	Albiglutide: 5.0 Liraglutide: 9.3	Albiglutide: 14.9 Liraglutide: 13.5	Symptomatic events: Albiglutide (10.4%) Liraglutide (13.0%) Major events: Albiglutide (Nil) Liraglutide (Nil)

GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycosylated hemoglobin; FPG, fasting plasma glucose; PPG, post prandial glucose; TEAE, treatment-emergent adverse event; GI, gastrointestinal; R, randomized; DB, double-blind; PC, placebo-controlled; PG, parallel-group; MC, multicentre; Nil, nothing; NS, not significant.

[a]Data presented are for 1.8 mg liraglutide dose.

there were none in the liraglutide groups. In the GetGoal-L-Asia study 42.9% of lixisenatide-treated patients and 23.6% of those receiving placebo reported symptomatic hypoglycemia; none of these events was severe [30]. When patients also receiving a sulfonylurea were excluded the incidence of hypoglycemia in the lixisenatide group was comparable to that in the placebo group (32.6% vs. 28.3%).

Gastrointestinal adverse events

The most frequently reported adverse events with GLP-1RAs are GI related and include nausea, vomiting, and diarrhea. Directly comparative (head-to-head) data are limited. For example, a study of lixisenatide versus liraglutide found that the incidences of nausea (23% vs. 22%) and vomiting (10% vs. 7%) were similar in both groups, whereas diarrhea was more common in the liraglutide group (16% vs. 3%) [40]. A recent meta-analysis sought to interrogate the data from randomised controlled trials with GLP-1RAs (liraglutide and exenatide) and assess the impact of different doses on GI adverse events [52]. Pairwise random-effects meta-analyses and mixed treatment comparisons found that, relative to placebo, exenatide 10 mg twice-daily is significantly more likely to cause nausea and vomiting whilst liraglutide 1.2 mg once a day is significantly more likely to cause diarrhea. However the meta-analysis included only liraglutide and exenatide and did not provide specific data on Asian patients.

As with efficacy, there is limited data on the GI tolerability of GLP-1RAs in Asian populations and even more so in Korean patients. The recent meta-analysis found that the RR of nausea (13.8 vs. 3.3, $P=0.100$) and vomiting (21.0 vs. 5.2, $P=0.205$) were numerically higher in Asians than in non-Asians but were not statistically significantly different [43]. Conversely, the RR of diarrhea was numerically, but not statistically, higher in non-Asians (1.7 vs. 2.6, $P=0.275$). In a Korean retrospective cohort analysis of patients who used exenatide, 23/143 (16.1%) had nausea and 17 (11.9%) suffered from vomiting [49]. These symptoms attenuated over time in the majority of patients. Only eight patients stopped taking exenatide due to anorexia or vomiting, all had above target HbA1c levels and were receiving two oral hypoglycemic agents but not insulin in the 3 months prior to study inclusion. Gao et al. [47] reported a similar safety profile with the use of exenatide in Asians as in non-Asian patients; nausea, which was generally mild-to-moderate, as the most common adverse event with exenatide (25% vs. 1% with placebo) [47]. A total of 64 subjects (7%) withdrew from the study by

Yang et al. [48] all but three of these patients were in the liraglutide treatment group. Adverse GI events, predominantly diarrhea, nausea, and vomiting led to the majority of these withdrawals. Amongst those GI adverse events most occurred within the first 4 weeks, were transient and decreased over time. In the HARMONY-7 study patients in the albiglutide group had more injection-site reactions and fewer GI adverse events than did those in the liraglutide group [50]. In the GetGoal-L-Asia study 61% of patients in the lixisenatide group reported having had a GI adverse event versus 14.6% in the placebo group; nausea occurred most frequently (39.6% of patients), followed by vomiting (18.9%) and diarrhea (6.5%) [30]. In this exclusively Asian population, the frequency of nausea was slightly higher than had been observed in global populations (39.6% vs. 22% to 25%).

Potential explanations for the higher incidence of GI adverse events amongst Asian patients include higher drug exposure due to the lower BMI of the participants (vs. non-Asian studies). However, this needs to be studied further. GI adverse events are generally transient; they tend to be higher during the first 2 weeks of treatment and often decrease with ongoing use [32,53]. Nevertheless, when such events are experienced in the early stages of treatment they have the potential to impact patient compliance [54]. To help with this, patients should be informed of the potential for these effects, including their likely duration, before treatment commences [55,56].

PRACTICAL CONSIDERATIONS FOR GLP-1RA USE IN KOREA

The available data, in global and Asian populations, support a number of benefits with the use of GLP-1RAs. These include a reduction HbA1c levels, weight maintenance or loss, and a relatively low risk of hypoglycemia. These benefits are offset against the propensity for GI adverse effects early in the course of treatment and a lack of long-term outcomes data [37].

Population statistics suggest that increasing age and obesity are key factors contributing to T2DM in Korea. In a cohort study involving 34,999 Korean men and women aged 30 to 59 years who were free of diabetes at baseline, metabolic health status, obesity, and weight change were all shown to be independently associated with increased incidence of T2DM over 5 years of follow-up [57]. Whilst the overall prevalence of diabetes in adults 30 years and older is 12.4%, it increases with age such that it affects 23.2% of Koreans aged 60 to 69 years and 25.9% of those aged 70 years or more. Half of all Koreans with

T2DM are obese (when defined as a BMI ≥25.0 kg/m^2 and a waist circumference >90 cm in men and >85 cm in women) with data showing the highest prevalence of obesity (63.6%) and abdominal obesity (57.6%) amongst those aged 40 to 49 years [5].

Given these statistics, treatment approaches that contribute to weight management such as the GLP-1RAs are becoming more relevant in the current management of T2DM in Korea. The inclusion of a prandial GLP-1RA into the treatment regimen of overweight patients with high HbA1c due to postprandial hyperglycemia is reasonable. Other clinical factors that may aid in treatment choice include uncontrolled HbA1c due to high postprandial (rather than fasting) blood glucose levels, need to control weight particularly amongst patients who already have a basal insulin as part of their regimen, patients at increased risk of hypoglycemia and patients with or at high risk of CV comorbidities, such as hypertension and fatty liver. The different pharmacodynamic features of GLP-1RAs may help guide the decision to administer a GLP-1RA with basal insulin; using short-acting lixisenatide or exenatide twice-daily in patients with prandial or postprandial hyperglycemia after near normalisation of fasting blood glucose and long-acting exenatide LAR, liraglutide, albiglutide or dulaglutide if the main concern is elevated fasting blood glucose levels [37].

GLP-1RAs are a relatively new treatment class in this population. Whilst Korean-specific data are limited, much progress has been made in understanding the full scope of their utility in the management of T2DM. Gaps in the literature that would warrant further research in the Korean population include the impact of GLP-1RA treatment on the recovery of insulin secretion, their effects on β-cell function and insulin sensitivity, whether they modulate improvements in endothelial dysfunction, their impact on lipid metabolism and any associations between their glucose lowering efficacy and GI side effects.

CONCLUSIONS

In concluding, we ask the question how does the above data help inform the optimal management of T2DM in Korea? The global data, in general, demonstrate that GLP-1RAs can contribute to patient management, providing beneficial reduction in HbA1c, without weight gain or hypoglycemia. More data are needed to examine efficacy, safety, and optimal dosing of GLP-1RAs in Korean patients with T2DM. However, based on the data currently available, their use is appropriate in several

patient groups, including patients whose HbA1c is uncontrolled, especially if this is due to postprandial glucose excursions and patients who are overweight or obese due to dietary problems (e.g., appetite control). Whether or not the potential for GI adverse events is increased in Asian patients, the possibility that it might occur should be explained to patients at treatment initiation to help maintain patient compliance.

CONFLICTS OF INTEREST

REFERENCES

1. Chan JC, Malik V, Jia W, Kadowaki T, Yajnik CS, Yoon KH, Hu FB. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. JAMA 2009;301:2129-40.
2. Hu FB. Globalization of diabetes: the role of diet, lifestyle, and genes. Diabetes Care 2011;34:1249-57.
3. Kim SM, Lee JS, Lee J, Na JK, Han JH, Yoon DK, Baik SH, Choi DS, Choi KM. Prevalence of diabetes and impaired fasting glucose in Korea: Korean National Health and Nutrition Survey 2001. Diabetes Care 2006;29:226-31.
4. Koo BK, Kim EK, Choi H, Park KS, Moon MK. Decreasing trends of the prevalence of diabetes and obesity in Korean women aged 30-59 years over the past decade: results from the Korean National Health and Nutrition Examination Survey, 2001-2010. Diabetes Care 2013;36:e95-6.
5. Kim CS, Ko SH, Kwon HS, Kim NH, Kim JH, Lim S, Choi SH, Song KH, Won JC, Kim DJ, Cha BY; Taskforce Team of Diabetes Fact Sheet of the Korean Diabetes Association. Prevalence, awareness, and management of obesity in Korea: data from the Korea national health and nutrition examination survey (1998-2011). Diabetes Metab J 2014;38:35-43.
6. Koo BK, Lee CH, Yang BR, Hwang SS, Choi NK. The incidence and prevalence of diabetes mellitus and related atherosclerotic complications in Korea: a National Health Insurance Database Study. PLoS One 2014;9:e110650.
7. Ko SH, Kim SR, Kim DJ, Oh SJ, Lee HJ, Shim KH, Woo MH, Kim JY, Kim NH, Kim JT, Kim CH, Kim HJ, Jeong IK, Hong EK, Cho JH, Mok JO, Yoon KH; Committee of Clinical Prac-

tice Guidelines, Korean Diabetes Association. 2011 Clinical practice guidelines for type 2 diabetes in Korea. Diabetes Metab J 2011;35:431-6.

8. Holst JJ, Vilsboll T. Combining GLP-1 receptor agonists with insulin: therapeutic rationales and clinical findings. Diabetes Obes Metab 2013;15:3-14.

9. Werner U. Effects of the GLP-1 receptor agonist lixisenatide on postprandial glucose and gastric emptying: preclinical evidence. J Diabetes Complications 2014;28:110-4.

10. Phillips LK, Prins JB. Update on incretin hormones. Ann N Y Acad Sci 2011;1243:E55-74.

11. Wong MC, Wang HH, Kwan MW, Zhang DD, Liu KQ, Chan SW, Fan CK, Fong BC, Li ST, Griffiths SM. Comparative effectiveness of dipeptidyl peptidase-4 (DPP-4) inhibitors and human glucagon-like peptide-1 (GLP-1) analogue as add-on therapies to sulphonylurea among diabetes patients in the Asia-Pacific region: a systematic review. PLoS One 2014;9:e90963.

12. Shyangdan DS, Royle P, Clar C, Sharma P, Waugh N, Snaith A. Glucagon-like peptide analogues for type 2 diabetes mellitus. Cochrane Database Syst Rev 2011;(10):CD006423.

13. Vilsboll T, Christensen M, Junker AE, Knop FK, Gluud LL. Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials. BMJ 2012;344:d7771.

14. Fineman MS, Cirincione BB, Maggs D, Diamant M. GLP-1 based therapies: differential effects on fasting and postprandial glucose. Diabetes Obes Metab 2012;14:675-88.

15. Lorber D. GLP-1 receptor agonists: effects on cardiovascular risk reduction. Cardiovasc Ther 2013;31:238-49.

16. Ratner R, Han J, Nicewarner D, Yushmanova I, Hoogwerf BJ, Shen L. Cardiovascular safety of exenatide BID: an integrated analysis from controlled clinical trials in participants with type 2 diabetes. Cardiovasc Diabetol 2011;10:22.

17. Marso SP, Lindsey JB, Stolker JM, House JA, Martinez Ravn G, Kennedy KF, Jensen TM, Buse JB. Cardiovascular safety of liraglutide assessed in a patient-level pooled analysis of phase 2: 3 liraglutide clinical development studies. Diab Vasc Dis Res 2011;8:237-40.

18. Morano S, Romagnoli E, Filardi T, Nieddu L, Mandosi E, Fallarino M, Turinese I, Dagostino MP, Lenzi A, Carnevale V. Short-term effects of glucagon-like peptide 1 (GLP-1) receptor agonists on fat distribution in patients with type 2 diabetes mellitus: an ultrasonography study. Acta Diabetol 2015 Jan 11 [Epub]. http://dx.doi.org/10.1007/s00592-014-0710-z.

19. Marso SP, Poulter NR, Nissen SE, Nauck MA, Zinman B, Daniels GH, Pocock S, Steinberg WM, Bergenstal RM, Mann JF, Ravn LS, Frandsen KB, Moses AC, Buse JB. Design of the liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results (LEADER) trial. Am Heart J 2013;166: 823-30.e5.

20. Gerich J. Pathogenesis and management of postprandial hyperglycemia: role of incretin-based therapies. Int J Gen Med 2013;6:877-95.

21. Ceriello A, Colagiuri S. International Diabetes Federation guideline for management of postmeal glucose: a review of recommendations. Diabet Med 2008;25:1151-6.

22. Rodbard HW, Blonde L, Braithwaite SS, Brett EM, Cobin RH, Handelsman Y, Hellman R, Jellinger PS, Jovanovic LG, Levy P, Mechanick JI, Zangeneh F; AACE Diabetes Mellitus Clinical Practice Guidelines Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus. Endocr Pract 2007; 13 Suppl 1:1-68.

23. American Diabetes Association. Standards of medical care in diabetes: 2011. Diabetes Care 2011;34 Suppl 1:S11-61.

24. DECODA Study Group; International Diabetes Epidemiology Group. Cardiovascular risk profile assessment in glucose-intolerant Asian individuals: an evaluation of the World Health Organization two-step strategy: the DECODA Study (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Asia). Diabet Med 2002;19:549-57.

25. DECODE Study Group on behalf of the European Diabetes Epidemiology Study Group. Will new diagnostic criteria for diabetes mellitus change phenotype of patients with diabetes? Reanalysis of European epidemiological data. BMJ 1998;317: 371-5.

26. Suh S, Joung JY, Jin SM, Kim MY, Bae JC, Park HD, Lee MS, Lee MK, Kim JH. Strong correlation between glycaemic variability and total glucose exposure in type 2 diabetes is limited to subjects with satisfactory glycaemic control. Diabetes Metab 2014;40:272-7.

27. Haimoto H, Sasakabe T, Umegaki H, Wakai K. Acute metabolic responses to a high-carbohydrate meal in outpatients with type 2 diabetes treated with a low-carbohydrate diet: a crossover meal tolerance study. Nutr Metab (Lond) 2009;6:52.

28. Kim MK, Suk JH, Kwon MJ, Chung HS, Yoon CS, Jun HJ, Ko JH, Kim TK, Lee SH, Oh MK, Rhee BD, Park JH. Nateglinide and acarbose for postprandial glucose control after optimizing fasting glucose with insulin glargine in patients with type 2 diabetes. Diabetes Res Clin Pract 2011;92:322-8.

29. Kim YG, Hahn S, Oh TJ, Kwak SH, Park KS, Cho YM. Differences in the glucose-lowering efficacy of dipeptidyl peptidase-4 inhibitors between Asians and non-Asians: a systematic review and meta-analysis. Diabetologia 2013;56:696-708.

30. Seino Y, Min KW, Niemoeller E, Takami A; EFC10887 GET-GOAL-L Asia Study Investigators. Randomized, double-blind, placebo-controlled trial of the once-daily GLP-1 receptor agonist lixisenatide in Asian patients with type 2 diabetes insufficiently controlled on basal insulin with or without a sulfonylurea (GetGoal-L-Asia). Diabetes Obes Metab 2012;14:910-7.

31. Becker RH, Stechl J, Msihid J, Kapitza C. Lixisenatide resensitizes the insulin-secretory response to intravenous glucose challenge in people with type 2 diabetes: a study in both people with type 2 diabetes and healthy subjects. Diabetes Obes Metab 2014;16:793-800.

32. Bolli GB, Owens DR. Lixisenatide, a novel GLP-1 receptor agonist: efficacy, safety and clinical implications for type 2 diabetes mellitus. Diabetes Obes Metab 2014;16:588-601.

33. Petersen AB, Christensen M. Clinical potential of lixisenatide once daily treatment for type 2 diabetes mellitus. Diabetes Metab Syndr Obes 2013;6:217-31.

34. Owens DR, Monnier L, Bolli GB. Differential effects of GLP-1 receptor agonists on components of dysglycaemia in individuals with type 2 diabetes mellitus. Diabetes Metab 2013;39:485-96.

35. Buse JB, Bergenstal RM, Glass LC, Heilmann CR, Lewis MS, Kwan AY, Hoogwerf BJ, Rosenstock J. Use of twice-daily exenatide in Basal insulin-treated patients with type 2 diabetes: a randomized, controlled trial. Ann Intern Med 2011;154:103-12.

36. Lorenz M, Pfeiffer C, Steinstrasser A, Becker RH, Rutten H, Ruus P, Horowitz M. Effects of lixisenatide once daily on gastric emptying in type 2 diabetes: relationship to postprandial glycemia. Regul Pept 2013;185:1-8.

37. Scholz GH, Fleischmann H. Basal insulin combined incretin mimetic therapy with glucagon-like protein 1 receptor agonists as an upcoming option in the treatment of type 2 diabetes: a practical guide to decision making. Ther Adv Endocrinol Metab 2014;5:95-123.

38. Drucker DJ, Buse JB, Taylor K, Kendall DM, Trautmann M, Zhuang D, Porter L; DURATION-1 Study Group. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. Lancet 2008;372:1240-50.

39. Buse JB, Rosenstock J, Sesti G, Schmidt WE, Montanya E, Brett JH, Zychma M, Blonde L; LEAD-6 Study Group. Liraglutide once a day versus exenatide twice a day for type 2 diabetes:

a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). Lancet 2009;374:39-47.

40. Kapitza C, Forst T, Coester HV, Poitiers F, Ruus P, Hincelin-Mery A. Pharmacodynamic characteristics of lixisenatide once daily versus liraglutide once daily in patients with type 2 diabetes insufficiently controlled on metformin. Diabetes Obes Metab 2013;15:642-9.

41. Meier JJ, Rosenstock J, Hincelin-Mery A, Roy-Duval C, Delfolie A, Coester HV, Forst T, Kapitza C. Effect of lixisenatide vs liraglutide on glycemic control, gastric emptying, and safety parameters in optimized insulin glargine T2DM ± metformin. Proceedings of American Diabetes Association 74th Scientific Sessions; 2014 Jun 13-17; San Francisco, CA. Alexandria (VA): American Diabetes Association; 2014.

42. Wysham C, Blevins T, Arakaki R, Colon G, Garcia P, Atisso C, Kuhstoss D, Lakshmanan M. Efficacy and safety of dulaglutide added onto pioglitazone and metformin versus exenatide in type 2 diabetes in a randomized controlled trial (AWARD-1). Diabetes Care 2014;37:2159-67.

43. Kim YG, Hahn S, Oh TJ, Park KS, Cho YM. Differences in the HbA1c-lowering efficacy of glucagon-like peptide-1 analogues between Asians and non-Asians: a systematic review and meta-analysis. Diabetes Obes Metab 2014;16:900-9.

44. Kadowaki T, Namba M, Imaoka T, Yamamura A, Goto W, Boardman MK, Sowa H. Improved glycemic control and reduced bodyweight with exenatide: a double-blind, randomized, phase 3 study in Japanese patients with suboptimally controlled type 2 diabetes over 24 weeks. J Diabetes Investig 2011;2:210-7.

45. Kadowaki T, Namba M, Yamamura A, Sowa H, Wolka AM, Brodows RG. Exenatide exhibits dose-dependent effects on glycemic control over 12 weeks in Japanese patients with suboptimally controlled type 2 diabetes. Endocr J 2009;56:415-24.

46. Kaku K, Rasmussen MF, Clauson P, Seino Y. Improved glycaemic control with minimal hypoglycaemia and no weight change with the once-daily human glucagon-like peptide-1 analogue liraglutide as add-on to sulphonylurea in Japanese patients with type 2 diabetes. Diabetes Obes Metab 2010;12:341-7.

47. Gao Y, Yoon KH, Chuang LM, Mohan V, Ning G, Shah S, Jang HC, Wu TJ, Johns D, Northrup J, Brodows R. Efficacy and safety of exenatide in patients of Asian descent with type 2 diabetes inadequately controlled with metformin or metformin and a sulphonylurea. Diabetes Res Clin Pract 2009;83:69-76.

48. Yang W, Chen L, Ji Q, Liu X, Ma J, Tandon N, Bhattacharyya A, Kumar A, Kim KW, Yoon KH, Bech OM, Zychma M. Liraglutide provides similar glycaemic control as glimepiride (both in

combination with metformin) and reduces body weight and systolic blood pressure in Asian population with type 2 diabetes from China, South Korea and India: a 16-week, randomized, double-blind, active control trial(*). Diabetes Obes Metab 2011; 13:81-8.

49. Shin J, Chang JS, Kim HS, Ko SH, Cha BY, Son HY, Yoon KH, Cho JH. Effects of a 6-month exenatide therapy on HbA1c and weight in Korean patients with type 2 diabetes: a retrospective cohort study. Diabetes Metab J 2012;36:364-70.

50. Prately RE, Nauck MA, Barnett AH, Feinglos MN, Ovalle F, Harman-Boehm I, Ye J, Scott R, Johnson S, Stewart M, Rosenstock J; HARMONY 7 study group. Once-weekly albiglutide versus once-daily liraglutide in patients with type 2 diabetes inadequately controlled on oral drugs (HARMONY 7): a randomised, open-label, multicentre, non-inferiority phase 3 study. Lancet Diabetes Endocrinol 2014;2:289-97.

51. Yun JS, Ko SH. Avoiding or coping with severe hypoglycemia in patients with type 2 diabetes. Korean J Intern Med 2015;30: 6-16.

52. Sun F, Yu K, Yang Z, Wu S, Zhang Y, Shi L, Ji L, Zhan S. Impact of GLP-1 receptor agonists on major gastrointestinal disorders for type 2 diabetes mellitus: a mixed treatment comparison meta-analysis. Exp Diabetes Res 2012;2012:230624.

53. Petersen AB, Knop FK, Christensen M. Lixisenatide for the treatment of type 2 diabetes. Drugs Today (Barc) 2013;49: 537-53.

54. Reid TS. Practical use of glucagon-like peptide-1 receptor agonist therapy in primary care. Clin Diabetes 2013;31:148-57.

55. Ratanawongsa N, Crosson JC, Schillinger D, Karter AJ, Saha CK, Marrero DG. Getting under the skin of clinical inertia in insulin initiation: the Translating Research Into Action for Diabetes (TRIAD) Insulin Starts Project. Diabetes Educ 2012;38: 94-100.

56. Kalra S, Kalra B. Counselling patients for GLP-1 analogue therapy: comparing GLP-1 analogue with insulin counselling. N Am J Med Sci 2012;4:638-40.

57. Jung HS, Chang Y, Eun Yun K, Kim CW, Choi ES, Kwon MJ, Cho J, Zhang Y, Rampal S, Zhao D, Soo Kim H, Shin H, Guallar E, Ryu S. Impact of body mass index, metabolic health and weight change on incident diabetes in a Korean population. Obesity (Silver Spring) 2014;22:1880-7.