Combination use of liraglutide and insulin to Japanese patients with multiple insulin injection: efficacy and cost

Sellami-Mnif Houda¹ · Umehara Toshihiro¹ · Yamazaki Yuriko¹ · Otake Hiroyuki¹ · Matoba Reie¹ · Sakashita Anna¹ · Matsuda Masafumi¹

Received: 15 February 2019 / Accepted: 29 June 2019 / Published online: 8 July 2019
© The Japan Diabetes Society 2019

Abstract

Objectives The introduction of liraglutide in the treatment of patients with type 2 diabetes already taking insulin is still subject to discussion in terms of timing and benefits. Gradually intensive insulin therapy is hastily prescribed. Switching from multiple insulin injection (MII) to insulin and liraglutide is evaluated in this study.

Methodology We studied 92 patients with type 2 diabetes previously under MII, C-peptide ≥ 1.5 ng/ml, divided into a group with reasonable glycemic control [RC: HbA1c $< 8\%$ (64 mmol/mol)] and another with a poor control [PC: HbA1c $\geq 8\%$, (64 mmol/mol)] after introduction of liraglutide and insulin therapy.

Results Except for HbA1c, there were no statistical differences between RC and PC groups. Basal insulin doses were adjusted to achieve the fasting plasma glucose of 90–120 mg/dl. HbA1c was significantly improved in both groups, from $9.6\% \pm 1.6$ (81 mmol/mol) and $7.0\% \pm 0.6$ (53 mmol/mol) to $8.0\% \pm 1.5$ (64 mmol/mol) and $6.8 \pm 0.5\%$ (51 mmol/mol). Reduction of body weight was significant only in RC (from 70 ± 16 kg to 68 ± 16 kg, $p < 0.01$). All patients from RC group and 58% of PC group reached HbA1c $< 8\%$ without hypoglycemia.

Conclusion This observation persuades us to propose the liraglutide and insulin combination to patients with C-peptide ≥ 1.5 ng/ml, regardless of the HbA1c.

Keywords Diabetes · Liraglutide · MMI therapy · Safety · Efficacy · C-peptide

Introduction

The prevalence of type 2 diabetes mellitus is rapidly increasing throughout the world. The World Health Organization cites the number of people living with type 2 diabetes has quadrupled in the past 34 years from 108 million in 1980 to 422 million in 2014 [1]. Every 6 s, a person dies from diabetes and/or diabetes-related complications (5.0 million deaths), and 12% of global health expenditure is spent on diabetes according to the International Diabetes Federation [2]. Type 2 diabetes is a worldwide health emergency with costly complications if not properly managed [3, 4]. The American Diabetes Association, the European Association for the Study of Diabetes, and the Japanese Society of Diabetes propose diabetes management guidelines and recommend gradually intensifying therapy starting with lifestyle changes and a single glucose-lowering agent [5]. However, even when diagnosed early, monotherapy is usually insufficient to bring a patient's blood glucose to recommended levels [6]. Taking multiple drugs, such as sulfonylureas,

✉ Sellami-Mnif Houda
houdasellami@yahoo.fr

Umehara Toshihiro
t.ume.tky@live.com

Yamazaki Yuriko
ue5ykwbr@gmail.com

Otake Hiroyuki
otake@saitama-med.ac.jp

Matoba Reie
blue_moonstar7@yahoo.co.jp

Sakashita Anna
annaanu2010@yahoo.co.jp

Matsuda Masafumi
matsudam@saitama-med.ac.jp

¹ Department of Endocrinology and Diabetes, Saitama Medical Center, Saitama Medical University, 1981 Kamoda, Kawagoe-shi, Saitama-ken 350-8550, Japan

thiazolidinediones, meglitinides, and insulin, may also expose patients to multiple side effects such as weight gain, hypoglycemia, and beta-cell burnout [7].

Recently, many pharmaceutical companies are introducing new medications with better glycemic reduction and side-effect balance, i.e., the DPP4 inhibitors (DPP4-I) and the Glucagon-like peptide1-receptor agonists (GLP1-RA). GLP1-RA was introduced in 2005 [8] and has since shown to have many promising benefits when compared to other glucose-lowering agents. In addition to decreasing glucose blood level, GLP1-RA action is strongly correlated to food intake; hypoglycemia risk is, therefore, reduced [9, 10]. GLP1-RA also inhibits glucagon secretion, decreases hepatic gluconeogenesis, improves insulin sensitivity, preserves beta cells [11, 12], slows gastric emptying [13], potentially promotes satiety and controls body weight in some studies [10–15]. Furthermore, the decrease of the glucagon release and delayed gastric emptying contribute to a better post-prandial glucose lowering as shown in patients' glucose monitoring (GM).

Compared with other anti-diabetic treatments, the efficacy and safety of combining GLP1-RA and basal insulin have been well established [16–18]. Moreover, the superiority of the combination of insulin and GLP1-RA to multiple insulin injection (MMI) has recently been shown [19]. Switching from MII usually reduces the frequency of injection and the risk of hypoglycemia, so the quality of life should also be improved.

In most surveys on liraglutide efficacy and safety, patients were taking high doses of GLP1-RA (from 1.8 to 3 mg/day) [20, 21]. In Japan, liraglutide was approved for use in 2010 by the Ministry of Health, Labor and Welfare, and the approved maximum dosage is only 0.9 mg/day which is half of that commonly used.

Since the introduction of liraglutide in Japan, several surveys have been conducted to evaluate the efficacy of the drug among the Japanese population. Some parameters have been suggested to predict high efficacy of liraglutide in Japanese patients: short duration of diabetes (less than 10 years), non-previous insulin therapy, low BMI, high HbA1c level at baseline [22, 23], and insulin secretion capacity: optimal cut-off values: fasting C-peptide: (F-CPR): 1.5 ng/ml, C-peptide index (CPI): 1.1 and urine C-peptide (U-CPR): 33.3 (1 g/day) seem to be useful predictors of liraglutide efficacy in type 2 diabetes [24].

The aim of this study is to analyze the efficacy of switching type 2 diabetes Japanese patients, previously under MII, to liraglutide and basal insulin in combination therapy. The patients are divided into high HbA1c group and reasonable HbA1c group. After 30 weeks, we will formulate hypotheses on predictive factors of efficiency. We will investigate whether there is a cost–benefit to switch from MII to insulin and liraglutide treatment.

Materials and method

Subjects

This is an observational retrospective study of Japanese patients with type 2 diabetes already under insulin therapy divided into two groups of patients: one group with a reasonable control [RC: HbA1c < 8% (64 mmol/mol)] and another group with a poor control [PC: HbA1c ≥ 8% (64 mmol/mol)], as 8% of HbA1c is the threshold to define the patients in need of new treatment strategy. The patients were monitored, between July 2015 and July 2016, at the outpatient department of the Saitama Medical Center in Saitama prefecture, Japan.

Inclusion and exclusion criteria

Eligibility criteria to switch patients, previously under MII, to liraglutide comprise the following: HbA1c and C-peptide levels, insulin need before liraglutide introduction, diabetes duration and the patient agreement, but the most relevant position to initiate liraglutide treatment is C-peptide level.

C-peptide level required to allow the switch from MII to liraglutide–insulin therapy was ≥ 1.5 ng/ml.

Patients started liraglutide injection at 0.3 mg/day, then 0.6 mg/day after 1 week, and 0.9 mg/day a week after. Patients were then strictly monitored first after 1 month, then every 3 months. The dose was maintained until the end of the study, only the doses of insulin were adjusted.

Patients were educated to adjust their insulin regarding their self-monitoring blood glucose (SMBG). Educators recommended the patients to monitor their blood glucose once in the morning. SMBG records were drawn at random.

Patients had an emergency number to call in case of need.

The treatment was adjusted, and in some cases, rapid-insulin was reintroduced when HbA1c was more than 8% (64 mmol/mol) in two blood checks.

The monthly cost (30 days) for the treatment was calculated at the university clinic (based on the Diabetes Resource Guide Japan 2015). The monthly cost included the standard prices of medicines (oral or injected), needles and SMBG (before injection's time) cost. Additional costs/test fees were excluded.

Statistical analyses

The data were manually extracted from electronic medical records. All the statistical analyses were performed using SPSS statistical software (IBM, USA). The descriptive statistics were calculated for all variables. The changes during the study period in the primary endpoint were analyzed

using a Chi squared test. Changes in HbA1c and insulin intake were compared with a baseline using *t* tests for the overall population.

- The primary objective of the study was to assess the effectiveness of liraglutide and insulin combination into two groups of patients with type 2 diabetes (PC group and RC group) previously under MII, but with reasonable C-peptide secretion.
- The secondary objectives were to compare the costs of liraglutide and the MII therapies and to investigate whether the C-peptide level may still be a helpful indicator of efficacy of liraglutide to patients previously under high doses of insulin.

Ethics statement

The protocol of this study was complied with the Declaration of Helsinki and was approved by the Ethics Review Board of the Saitama Medical University IRB, Japan. Approval number: 1764, issued on 5 October 2017. The study has retrospective design and as it was part of standard clinical practice; no written informed consent was required.

Results

Patients characteristics

Our study covers 92 patients with type 2 diabetes who have switched from MII therapy to liraglutide–basal insulin therapy (divided into 45 men and 47 women). All patients are over 20 years with a mean age of 59 ± 13 years. The average level of HbA1c is $8.3 \pm 1.8\%$ (67 mmol/mol). The diabetes's duration is 12.9 ± 8.2 years and the C-peptide level for all patients is 1.9 ± 1.3 ng/ml.

We divided the patients into two groups:

1. Group 1: [RC: HbA1c < 8% (64 mmol/mol)]: 47 subjects.
2. Group 2: [PC: HbA1c $\geq$ 8% (64 mmol/mol)]: 45 subjects.

The characteristics of the two groups are shown in Table 1.

Table 1 Clinical and biochemical characteristics of patients divided according to HbA1c

	All	<i>n</i>	Poor control group	<i>n</i>	Reasonable control group	<i>n</i>
N (M/F)	92 (45/47)		45 (22/23)		47 (23/24)	
Age (years old)	59.3 ± 12.6		57.4 ± 14.2		61.2 ± 10.7	
Duration of diabetes (years)	12.9 ± 8.2		12.3 ± 8.5		13.5 ± 8.0	
C-peptide index	1.9 ± 1.3		1.6 ± 1.1		2.1 ± 1.4	
BMI (kg/m ²)	27.7 ± 5.5		27.9 ± 4.7		27.5 ± 6.1	
HbA1c (%)	8.3 ± 1.8 (67 mmol/mol)		9.6 ± 1.6 (81 mmol/mol)		7.0 ± 0.6 (53 mmol/mol)	
LDL-Chol (mg/dl)	96.4 ± 38.2		94.3 ± 46.0		98.4 ± 29.2	
HDL (mg/dl)	44.9 ± 14.8		42.9 ± 18.0		46.9 ± 10.6	
TG (mg/dl)	201 ± 338		237 ± 475		166 ± 88	
Cr (mg/dl)	0.9 ± 1.1		0.8 ± 0.6		1.1 ± 1.4	
Sys BP (mmHg)	138 ± 19		139 ± 21		138 ± 18	
Dias BP (mmHg)	78 ± 15		80 ± 18		75 ± 12.8	
Basal insulin (U/day)	17.0 ± 14.0	81	16.3 ± 14.5	40	17.7 ± 13.1	41
Glargine (U/day)	18.1 ± 16.0	26	17.9 ± 16.4	12	18.3 ± 16.3	14
Degludec (U/day)	15.9 ± 12.9	47	15.3 ± 14.0	21	16.5 ± 11.9	26
Detemir (U/day)	19.3 ± 14.4	8	16.3 ± 12.7	7	40.0 ± 0.0	1
Bolus insulin (U/day)	21.8 ± 13.6	56	26.5 ± 17.9	19	19.4 ± 10.5	37
Injection Freq/day	2.8 ± 1.5		2.3 ± 1.5		3.3 ± 1.3	
Timing/day	2.2 ± 1.1		1.9 ± 1.2		2.5 ± 0.9	
Liraglutide ^a (mg/day)	0.9 ± 0.1	7	0.8 ± 0.1	5	0.9 ± 0.0	2

All patients who received DPP4 inhibitors (alogliptin: 1, vildagliptin: 8, sitagliptin: 5, teneligliptin: 3, linagliptin: 5) stopped using them

^aPatients were taking liraglutide just shortly before our survey. Clinical application of combination use of liraglutide and insulin had not been approved by health care services provided by health insurance in Japan until 2014. No significant difference in data was shown by mean $\pm$ SD. The observational period was 272 ± 101 days ($n=92$ otherwise stated). All the subjects were under combined treatment of liraglutide and insulin for an observational period. One received 30 mix insulin, five received lixisenatide (PC: 4; RC: 1), and two received exenatide (PC: 1; RC: 1)

The observational period was 272 ± 101 days. Throughout the study, the doses of basal insulin were adjusted to achieve the fasting plasma glucose (PG) of 90–120 mg/dl.

A few patients from the PC group were taking bolus insulin comparing to the RC group: 19/37. This difference was not significant.

The dose of liraglutide was increased from 0.3 to 0.9 mg/day. The maximum permitted dosage of liraglutide is 0.9 mg/day in Japan.

The efficacy of liraglutide

HbA1c decreased significantly at the end of the observation in both groups (Table 2). However, there was better improvement of HbA1c in the PC group when compared to the RC group [$9.6\% \pm 1.6$ (81 mmol/mol) to $8.0\% \pm 1.5$ (64 mmol/mol) versus $7.0\% \pm 0.6$ (53 mmol/mol) to $6.8\% \pm 0.5$ (51 mmol/mol)].

After the introduction of 0.9 mg of liraglutide, patients needed significantly more basal insulin, to reach the blood glucose target: 21.1 ± 12.1 U/day and 20.5 ± 13.0 U/day for the PC and the RC groups, respectively (Table 2). The average daily insulin injections decreased, as rapid-insulin need was reduced.

No severe complications or side effects were observed; however, patients reported less anxiety regarding hypoglycemia after switching treatment.

Weight loss

In our survey, we observed a significant reduction of body weight only in the RC group (from 70 ± 16 to 68 ± 16 kg, $p < 0.01$ versus before). In the PC group, body weight changed from 73 ± 14 to 75 ± 16 kg.

C-peptide level

At the end of the observation, we noticed that the CPIs were reversely correlated with HbA1c levels, as suggested by the R^2 linear regression test (Fig. 1: basal C-peptide index and HbA1c level at the end of the observation)

$$\text{HbA1c} = 7.96 - 0.30 \times \text{CPI}; r^2 = 0.083, p < 0.05.$$

The cost efficacy

After 1 year of liraglutide, the average cost for medicine, needles, SMBG, visits and instruction per month increased in our study group from $37,002 \pm 15,127$ to $41,549 \pm 12,442$

Table 2 Comparison of some clinical and biochemical results before and after treatment switch within the two study groups

Poor control group	Before	<i>n</i>	At the end of observation	<i>n</i>
HbA1c (%)	9.6 ± 1.6 (81 mmol/mol)	45	8.0 ± 1.5 (64 mmol/mol)	45*
Basal insulin (U/day)	16.3 ± 14.5	40	21.1 ± 12.1	45*
Glargine (U/day)	17.9 ± 16.4	12	16.3 ± 16.3	12
Degludec (U/day)	15.3 ± 14.0	21	21.9 ± 11.0	28
Detemir (U/day)	16.3 ± 12.7	7	26.0 ± 9.1	7
Bolus insulin (U/day)	26.5 ± 17.9	19	7.0 ± 0.0	1*
Injection Freq/day	2.3 ± 1.5	45	2.2 ± 0.7	45*
Timing/day	1.9 ± 1.2	45	1.2 ± 0.5	45*
Liraglutide (mg/day)	0.8 ± 0.1	5	0.9 ± 0.1	45
Reasonable control group	Before	<i>n</i>	At the end of observation	<i>n</i>
HbA1c (%)	7 ± 0.6 (53 mmol/mol)	47	6.8 ± 0.5 (51 mmol/mol)	47*
Basal insulin (U/day)	17.7 ± 13.1	41	20.5 ± 13.0	47*
Glargine (U/day)	18.3 ± 16.3	14	21.2 ± 14.8	16
Degludec (U/day)	16.5 ± 11.9	26	19.5 ± 12.5	30
Detemir (U/day)	40.0 ± 0.0	1	40.0 ± 0.0	1
Bolus insulin (U/day)	19.4 ± 10.5	37	3.5 ± 13.6	3*
Injection Freq/day	3.3 ± 1.3	47	2.2 ± 0.7	47*
Timing/day	2.5 ± 0.9	47	1.1 ± 0.4	47*
Liraglutide (mg/day)	0.9 ± 0.0	2	0.8 ± 0.2	47

n number of patients

* $p < 0.05$ versus before

Fig. 1 Basal C-peptide index and HbA1c level at the end of the observation. RC group, PC group

Japanese yen/month (+13%). The overall cost, however, decreased for some patients who decreased their daily SMBG, needles used per day, insulin need, and also, stopped DPP4-Is. Furthermore, 64.1% of patients decreased their daily SMBG after switching from MII to liraglutide and insulin. After the introduction of liraglutide and insulin adjustment, 69.5% of all patients used the same number of needles or less.

Discussion

In our study, liraglutide was also efficient for patients who were in need of insulin and already under MII. Liraglutide efficacy was significant in both RC and PC groups. Weight loss, however, was not significant at the end of study. Our hypothesis whether C-peptide is a good indicator of liraglutide efficacy within the Japanese population seems plausible as patients with higher C-peptide had better improvements in HbA1c.

Efficacy and side effects

Numerous anti-diabetes agents including sulfonylureas, thiazolidinediones, and obviously basal and rapid-action insulins are associated with increased risk of severe hypoglycemic episodes, weight gain [25, 26, 30] and beta-cell burnout [7]. In contrast, GLP1-RA are more likely beta-cell conservative [31, 32] and are correlated with low risk of hypoglycemia (severe and non-severe) [9, 10] and greater weight loss [10]. That may press us to discuss whether we should consider GLP1-RA more often before starting an insulin-therapy intensification.

Recently, the effectiveness of combining basal insulin and GLP1-RA versus MII on glycemic control has been shown [difference in means: -0.48% (95% CI -0.67 to -0.30);

$p < 0.0001$], weight loss [difference in means: -2.60 kg (95% CI -3.32 to -1.89); $p < 0.0001$] and non-severe hypoglycemic episodes [Odds Ratio (OR) 0.27 (95% CI 0.07–1.11); $p = 0.07$] [19]. Our survey argues switching from MII to liraglutide therapy provides better glycemic control assessed by HbA1c level reduction. Our findings are consistent for both groups: patients with poor glycemic control and patients with reasonable glycemic control.

Despite increase in basal insulin daily injection in both groups, no severe hypoglycemia was reported. However, we should keep in mind that GLP1-RA may also be associated with some side effects, some mild-to-severe hypoglycemia episodes were reported in the literature, but mostly when GLP1-RA is taken with sulfonylureas or insulin [10–19, 29]. Additionally, gastrointestinal issues [10–34], and cases of acute pancreatitis have been reported on some surveys on exenatide, but there are no side effect-related studies on liraglutide [10–35].

Weight loss

Liraglutide weight loss has been well established in Caucasian populations, where the degree of obesity and insulin resistance is considerably high [8, 10]. Appetite suppression, weight loss, and insulin-resistance decrease, associated with the stimulation of insulin secretion seem to be the main keys of blood glucose and HbA1c improvement. In our survey, performed in the Japanese population, HbA1c improved in both groups, but weight decreased only in the RC group (by 2 kg) and increased in the PC group. However, we recognize the limitations of having a small population size in each group. In general, studies performed with Japanese patients using liraglutide show varied results in terms of weight effects. Some studies showed that liraglutide results in weight reduction, other studies have, however, shown that body weight remained unchanged [17, 36]. Interestingly, Daisuke Ito observed that liraglutide effect on weight was greatest within non-obese Japanese patients (BMI less than 25). In contrast, obese patients (BMI of 35 kg/m² and more) had undesirable weight gain after 6 months of 0.9 mg of liraglutide [36]. In our survey, we did not have the diet records of all the patients, but none had reported a noticeable change in appetite. Some reasons may explain the difference of weight trends between the two groups: in the PC group, liraglutide did increase the insulin secretion, suppress glucagon release, but had no effect on appetite. Thus, the amount of carbohydrate ingested, previously eliminated in urine, was stored after liraglutide intake, resulting in weight gain.

If we analyze the PC group from another point of view, despite the weight gain, HbA1c did decrease within our Japanese population. In some comparative studies between Caucasians and Japanese and East Asian populations, type 2 diabetes is triggered differently within the two populations.

Caucasian type 2 diabetes patients have higher insulin resistance and β -cell response, as indicated by the homeostatic-model assessment of insulin resistance (HOMA-IR), the homeostatic-model assessment of β -cell function (HOMA- β) and the insulinogenic index (IGI). In East-Asia and Japan, type 2 diabetes onset is characterized by an impaired insulin secretion with lower insulin resistance; lower HOMA-IR, HOMA- β and IGI [37, 38]. Pathophysiological mechanisms of type 2 diabetes within populations are different; it is entirely plausible that the mechanism of liraglutide also is different between populations and ethnicities. Moreover, some studies have shown that incretin-based therapies are more effective within East Asian patients compared to Caucasians by improving post-prandial β cell secretion [39]. Furthermore, it has been demonstrated that special food intake (eating more fish and less meat), likely more similar to the East Asian diet, ameliorates the efficacy of incretin-based therapies in HbA1c by enhancing GLP-1 secretion [39].

Beta cells and antibody formation

Unfortunately, type 2 diabetes is often diagnosed late, when almost 50% of beta-cell functions are already lost [28]. Some common oral diabetes drugs are ineffective against beta cells cytokine-induced apoptosis [29] which would increase insulin deficiency, basal and rapid-insulin therapy needs and side effects [30, 31]. This makes beta-cell conservation a daily challenge. To slow down the apoptosis process, some clinical trials have demonstrated the efficacy of GLP1-RA use to conserve beta-cell reserves [31, 32]. In contrast, some GLP1-RA may induce antibody formation, for patients using exenatide [29], but with no effect on the HbA1c reduction in patients using liraglutide.

In our survey, we found that HbA1c improved better within patients with higher C-peptide. The C-peptide level was basically the main inclusion criterion for the patients initially under insulin.

Cost

The monthly cost of liraglutide therapy increased in our study by approximately 13%. However, in some patients, the monthly cost of switching treatment from MII to liraglutide and insulin decreased. These patients also decreased their insulin, needle, and daily SMBG needs after liraglutide introduction. No patient reported noticeable hypoglycemia after the introduction of liraglutide. As GLP1-RA action is glucose dependent, the risk of hypoglycemia is considerably less than other medications [9, 10]. That may explain why some patients, mostly from the RC group, decreased their daily SMBG. And although daily SMBG decreased, HbA1c also decreased without

hypoglycemia in all our patients. GLP1-RA cost itself is quoted as high regarding American Diabetes Association [6], compared to metformin, sulfonylurea and insulin. However, we need to consider that in some cases, it is less costly than MII therapy.

Conclusion

The present study supports the efficacy and safety of insulin and GLP1-RA (liraglutide) therapy for Japanese patients with reasonable C-peptide secretion, previously under MII. Moreover, at the end of the study, we found that the efficacy of liraglutide was significant for patients with moderate-to-high HbA1c. Despite the high cost of liraglutide treatment, patients with a moderate need for insulin were paying less after switching their treatment. The findings may suggest that patients with type 2 diabetes previously under MII can have better glycemic control with less complications and costs after switching to insulin and liraglutide therapy. C-peptide could be an interesting indicator of liraglutide efficacy even to patients under MII therapy.

Study limitations

- Our results are limited to the Japanese population
- As an observational retrospective study, our results are assessing potential relation between C-peptide and GLP1-RA efficiencies.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Compliance with ethical standards

Conflict of interest Matsuda Masafumi MD, Ph.D.: potential competing financial interest and association with commercial entities, cited below, that could be viewed as having an interest in the general area of the submitted manuscript: AstraZeneca Corporation, Sanofi Co., Ltd., Novo Nordisk Pharma Co., Ltd., Takeda Pharmaceutical Co., Ltd., Astellas Pharma Inc., Eli Lilly Co., Ltd., Mitsubishi Tanabe Co., Ltd., Ono Pharmaceutical Co., MSD Corporation, Novartis Pharma Corporation, Japan Boehringer Ingelheim Pharmaceutical Co., Ltd. Sellami-Mnif Houda MD has no competing interests to declare. Toshihiro Umehara MD, Ph.D. has no competing interests to declare. Yamazaki Yuriko MD has no competing interests to declare. Hiroyuki Otake MD, Ph.D. has no competing interests to declare. Tomoko Morita MD, Ph.D. has no competing interests to declare. Matoba Reie MD has no competing interests to declare. Sakashita Anna MD has no competing interests to declare.

References

- World Health Organization. Global report on diabetes. Geneva: World Health Organization; 2016.
- International Diabetes Federation. IDF diabetes atlas. 6th ed. Brussels: International Diabetes Federation; 2014. <http://dro.deakin.edu.au/view/DU:30060687>.
- Seuring T, Archangelidi O, Suhrcke M. The economic costs of type 2 diabetes: a global systematic review. *Pharmacoeconomics*. 2015;33:811–31.
- Hex N, Bartlett C, Wright D, Taylor M, Varley D. Estimating the current and future costs of type 1 and type 2 diabetes in the UK, including direct health costs and indirect societal and productivity costs. *Diabet Med*. 2012. <https://doi.org/10.1111/j.1464-5491.2012>.
- Hiroshi I, Nobuya I, Kohjiro U, Haruhiko O, Hideki K, Disuke K, Yasushi T, Narihito Y, Satoshi I. Treatment guide for diabetes. Japan Diabetes Society; 2014–2015.
- American Diabetes Association. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes 2018. *Diabetes Care*. 2018;41(Supplement 1):S73–85.
- Donath MY, Ehses JA, Maedler K, Schumann DM, Ellingsgaard H, Eppler E, Reinecke M. Mechanisms of beta-cell death in type 2 diabetes. *Diabetes*. 2005;54(Suppl 2):108–13.
- 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(9548):1696–705.
- Qualmann C, Nauck MA, Holst JJ, Orskov C, Creutzfeldt W. Insulinotropic actions of intravenous glucagon-like peptide-1 (GLP-1) [7–36 amide] in the fasting state in healthy subjects. *Acta Diabetol*. 1995;32:13–6.
- Prasad-Reddy L, Isaacs D. A clinical review of GLP-1 receptor agonists: efficacy and safety in diabetes and beyond. *Drugs Context*. 2015;4:212–83.
- Drucker DJ. Enhancing incretin action for the treatment of type 2 diabetes. *Diabetes Care*. 2003;26(10):2929–40.
- Wajchenberg BL. β -cell failure in diabetes and preservation by clinical treatment. *Endocr Rev*. 2007;28(2):187–218.
- Wettergren A, Schjoldager B, Mortensen PE, Myhre J, Christiansen J, Holst JJ. Truncated GLP-1 (proglucagon 78–107-amide) inhibits gastric and pancreatic functions in man. *Dig Dis Sci*. 1993;38:665–73.
- Larsen PJ, Fledelius C, Knudsen LB, Tang-Christensen M. Systemic administration of the long-acting GLP-1 derivative NN2211 induces lasting and reversible weight loss in both normal and obese rats. *Diabetes*. 2001;50:2530–9.
- Donahey JCK, Van Dijk G, Woods SC, Seeley RJ. Intraventricular GLP-1 reduces short but not long-term food intake or body weight in lean and obese rats. *Brain Res*. 1998;779:75–83.
- Eng C, Kramer CK, Zinman B, Retnakaran R. Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis. *Lancet*. 2015;384(9961):2228–34.
- Seino Y, Kaneko S, Fukuda S, Osonoi T, Shiraiwa T, Nishijima K, Kaku K. OP72 Combination therapy with liraglutide and insulin in Japanese subjects with type 2 diabetes: the LIRA-ADD2INSULIN JAPAN trial. *Diabetes Res Clin Pract*. 2014. [https://doi.org/10.1016/S0168-8227\(14\)70278-5](https://doi.org/10.1016/S0168-8227(14)70278-5).
- Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JFE, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB, LEADER Steering Committee, LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375:311–22.
- Wysham CH, Lin J, Kuritzky L. Safety and efficacy of a glucagon-like peptide-1 receptor agonist added to basal insulin therapy versus basal insulin with or without a rapid-acting insulin in patients with type 2 diabetes: results of a meta-analysis. *Postgrad Med*. 2017. <https://doi.org/10.1080/00325481.2017.1297669>.
- 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. <https://doi.org/10.1016/j.ahj.2013.07.012>.
- Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, Lau DCW, le Roux CW, Violante Ortiz R, Jensen CB, Wilding JPH. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. *N Engl J Med*. 2015;373:11–22.
- Toyoda M, Yokoyama H, Abe K, Nakamura S, Suzuki D. Predictors of response to liraglutide in Japanese type 2 diabetes. *Diabetes Res Clin Pract*. 2014;106(3):451–7.
- Ito D, Iuchi T, Kurihara S, Inoue I, Katayama S, Inukai K. Efficacy and clinical characteristics of liraglutide in Japanese patients with type 2 diabetes. *J Clin Med Res*. 2015;7(9):694–9.
- Kozawa J, Inoue K, Iwamoto R, Kurashiki Y, Okauchi Y, Kashine S, Kitamura T, Maeda N, Okita K, Iwahashi H, Funahashi T, Imagawa A, Shimomura I. Liraglutide is effective in type 2 diabetic patients with sustained endogenous insulin-secreting capacity. *J Diabetes Investig*. 2012. <https://doi.org/10.1111/j.2040-1124.2011.00168.x>.
- Holman RR, Thorne KI, Farmer AJ, et al. Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. *N Engl J Med*. 2007;357:1716–30.
- Rys P, Wojciechowski P, Siejka S, Małeck P, Hak L, Malecki MT. A comparison of biphasic insulin aspart and insulin glargine administered with oral antidiabetic drugs in type 2 diabetes mellitus—a systematic review and meta-analysis. *Int J Clin Pract*. 2014;68(3):304–13.
- Reid T, Gao L, Gill J, Stuhr A, Traylor L, Vlajnic A, Rhinehart A. How much is too much? Outcomes in patients using high-dose insulin glargine. *Int J Clin Pract*. 2016;70(1):56–65.
- Mayfield JA, White RD. Insulin therapy for type 2 diabetes: rescue, augmentation, and replacement of beta-cell function. *Am Fam Physician*. 2004;70(3):489–500.
- Garber AJ. Long-acting glucagon-like peptide 1 receptor agonists: a review of their efficacy and tolerability. *Diabetes Care*. 2011;34(2):S279–84.
- Donner T, Sarkar S. Insulin—pharmacology, therapeutic regimens, and principles of intensive insulin therapy. In: Feingold KR, Anawalt B, Boyce A, et al., editors. *Endotext* [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000. <https://www.ncbi.nlm.nih.gov/books/NBK278938/>. Accessed 23 Feb 2019.
- Cefalu WT, Buse JB, Del Prato S, Home PD, LeRoith D, Nauck MA, Raz I, Rosenstock J, Riddle MC. Beyond metformin: safety considerations in the decision-making process for selecting a second medication for type 2 diabetes management: reflections from a diabetes care editors' expert forum. *Diabetes Care*. 2014;37(9):2647–59.
- Drucker DJ. The biology of incretin hormones. *Cell Metab*. 2006;3:153–65.
- Nauck M, Frid A, Hermansen K, et al. LEAD-2 Study Group. 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.
- Rosenstock J, Brazg R, Andryuk PJ, Lu K, Stein P. Sitagliptin Study 019 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing pioglitazone therapy in patients with type 2 diabetes: a 24-week, multicenter, randomized,

- double-blind, placebo-controlled, parallel-group study. *Clin Ther*. 2006;28:1556–68.
35. 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(5):1013–22.
 36. Seino Y, Rasmussen MF, Zdravkovic M, Kaku K. Dose-dependent improvement in glycemia with once-daily liraglutide without hypoglycemia or weight gain: a double-blind, randomized, controlled trial in Japanese patients with type 2 diabetes. *Diabetes Res Clin Pract*. 2008;81(2):161–8.
 37. Fukushima M, et al. Insulin secretion capacity in the development from normal glucose tolerance to type 2 diabetes. *Diabetes Res Clin Pract*. 2004;66(Suppl 1):S37–43.
 38. Chan JC, et al. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *JAMA*. 2009;301:2129–40.
 39. Yabe D, Kuwata H, Iwasaki M, Seino Y. Why are incretin-based therapies more efficient in East Asian? Perspectives from the pathophysiology of type 2 diabetes and East Asian dietary habits. *EMJ Diabet*. 2015;3(1):57–65.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.