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ORIGINAL ARTICLE

The efficacy of once-daily liraglutide as an add-on to oral antidiabetic agents on weight reduction and glycemic control in obese patients with inadequately controlled type 2 diabetes: a retrospective analysis in relation to liraglutide dose escalation within a 7-month treatment period

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Abstract

Background This study aimed to evaluate the efficacy of once-daily liraglutide as an add-on to oral antidiabetics (OADs) on glycemic control and body weight in obese patients with inadequately controlled type 2 diabetes (T2D).

Methods A total of 27 obese T2D patients who received 7 months (0.6 mg/day for the first month, 1.2 mg/day for 3 months, and 1.8 mg/day for 3 months) of liraglutide treatment as an add-on to OADs were included. Data on body weight (kg), fasting plasma glucose (FPG, mg/dL), postprandial glucose (PPG, mg/dL), and HbA1c (%), were recorded.

Results Liraglutide doses of 1.2 mg/day and 1.8 mg/day were associated with significant decreases in body weight (by 8.0% and 11.9%, respectively, $p < 0.01$ for each) and HbA1c (by 20.0 and 26.5%, respectively, $p < 0.01$), while all liraglutide doses yielded significant reductions in FPG (p ranging from < 0.001 to < 0.01) and PPG (p ranging from < 0.001 to < 0.01). Glycemic parameters showed a significant reduction from the 1.2 mg/day dose to the 1.8 mg/day dose ($p < 0.01$ for each), whereas no further reduction in body weight was noted.

Conclusion Our findings indicate favorable efficacy of liraglutide as an add-on to OADs in weight reduction and improving glycemic parameters in obese patients with inadequately controlled T2D. Once-daily liraglutide treatment was associated with significant weight loss and improved HbA1c levels only at 1.2-mg and 1.8-mg doses, while a 1.8-mg dose compared with a 1.2-mg dose seemed to enable a further improvement in glycemic control but not in weight loss.

Keywords Type 2 diabetes mellitus · Glycemic control · HbA1c target · Obesity · Body weight · Liraglutide · Dose titration · Iraq

Introduction

Despite the availability of a variety of treatment options, a considerable proportion of patients with type 2 diabetes (T2D) worldwide have suboptimal glycemic control with failure to achieve glycated hemoglobin (HbA1c) targets [1], and this is more common in Arabian Gulf countries or the Middle East and North Africa (MENA) region [2–4] than in the USA or European countries [1].

In a past study conducted in 2008 with 3395 T2D patients from Iraq, poor glycemic control (HbA1c ≥ 7%) was noted in 2571 (75.7%) patients, and most of the patients stated that the current health situation in Iraq (i.e., no drug supply at the primary health care center or a drug shortage, drug or

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laboratory expenses, or migration after war) was the cause of their poor glycemic control [5]. Nonetheless, rates for poor glycemic control remained unchanged in the following years in Iraq and were reported to be 83.6% ($n = 337$, HbA1c: 10.1%, duration of diabetes: 8.7 years) in 2013 [6] and 82% ($n = 100$, HbA1c: 8.4%, duration of diabetes: 8.0 years) in 2018 [7]. This seems notable given that consistent with worldwide trends for the prevalence of diabetes mellitus [8], diabetes has reached an epidemic status in Iraq over the last decade, with a dramatic (115%) increase from 19.58/1000 in 2000 to 42.27/1000 in 2015 [9].

Glucagon-like peptide 1 (GLP-1) is an incretin hormone responsible for glucose-dependent stimulation of insulin secretion and the inhibition of glucagon secretion, while it also delays gastric emptying and induces satiety, leading to decreased energy intake and weight reduction [10, 11]. In this regard, GLP-1 analogs with receptor agonist (RA) activity have emerged as effective antidiabetic treatments; they are recommended by recent guidelines to be preferred following metformin, particularly in adults with T2D and additional CV risk factors, given their potential to meet the criteria of optimal T2D treatment involving patient-oriented treatment goals (i.e., reduced risk of weight gain, hypoglycemia and CV complications) beyond glycemic control [12, 13].

Liraglutide is a long-acting GLP-1RA with an effect on both fasting glucose (via enhanced glucose-dependent insulin secretion and reduced glucagon secretion in the fasting state) and postprandial glucose (via enhanced postprandial insulin secretion and the inhibition of glucagon secretion) [14, 15]. Accordingly, along with its unique therapeutic potential enabling glycemic control with no risk of hypoglycemia and the additional benefit of weight loss, liraglutide is considered a preferable noninsulin injectable agent both in obesity and in T2D [15–17].

Liraglutide was approved by the FDA in January 2010 as a once-daily injection for patients with uncontrolled T2D despite lifestyle changes and metformin monotherapy, while after the demonstration of CV benefits in high-risk patients by the LEADER trial, it was also approved by the FDA for reducing 3-point major adverse cardiac events [14, 18].

This study was designed to evaluate the efficacy of once-daily liraglutide as an add-on to oral antidiabetics (OADs) in escalated doses of 0.6 mg, 1.2 mg, and 1.8 mg through a 7-month treatment period on glycemic control and body weight reduction in obese patients with inadequately controlled T2D in Iraq.

Methods

Study population

A total of 27 obese T2D patients (mean age: 48 years, ranging from 32 to 68 years, 51.9% were males) who received 7-month liraglutide treatment as an add-on to OADs due to failure to achieve glycemic control and weight reduction on previous OADs (metformin with or without dipeptidyl peptidase-4 inhibitors (DPP-4i) or glimepiride) were included in this retrospective study conducted between January 2017 and August 2017.

While the present study was exempt from the requirements of ethical approval because of its retrospective design, the study was conducted in full accordance with local Good Clinical Practice guidelines and current legislation, and permission was obtained from our institutional ethics committee for the use of patient data for publication purposes.

Liraglutide treatment

The trial consisted of a 1-month starting dose (0.6 mg/day) period and two consecutive 3-month escalation periods for 1.2 mg/day and 1.8 mg/day doses of once-daily subcutaneous liraglutide therapy. Accordingly, the study period included an overall 7-month liraglutide treatment, with a starting dose of 0.6 mg/day to avoid nausea and vomiting for the first 1 month, escalation to 1.2 mg for the next 3 months, and a final escalation to the maximum permissible dose of 1.8 mg daily for 3 months.

Assessments

Data on patient demographics (age, sex) and the duration of diabetes were recorded at baseline. Data on body weight (kg) and glycemic parameters, including fasting plasma glucose (FPG, mg/dL), postprandial glucose (PPG, mg/dL), and HbA1c (%), were recorded at baseline and at three consecutive visits conducted at month 1 (after 1 month of the 0.6 mg/day treatment), month 4 (after 3 months of the 1.2 mg/day treatment), and month 7 (after 3 months of the 1.8 mg/day treatment) of liraglutide treatment. Changes from baseline in body weight and glycemic parameters were evaluated for the 0.6 mg, 1.2 mg, and 1.8 mg daily doses, while changes in these parameters from the 1.2-mg dose were also evaluated during the 1.8-mg dose treatment period.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA). Changes over time are evaluated by dependent group t test or Wilcoxon test depending on the distribution pattern of continuous variables. Data were expressed as the "mean (standard deviation, SD)," minimum-maximum and percent (%) where appropriate. $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics

The mean patient age was 48 years (range, 32 to 68 years), and males composed 51.9% of the study population. The duration of diabetes was less than 5 years in 51.9% of patients, while 18.5% of patients had suffered from diabetes for more than 10 years (Table 1).

The baseline average values for body weight and HbA1c were 113.9 kg (ranging from 80 to 180 kg) and 9.8% (ranging from 7.5 to 14.0%), respectively (Table 1).

Effect of 7-month liraglutide treatment on body weight and glycemic parameters

For body weight, a significant decrease from baseline was noted with liraglutide doses of 1.2 mg/day and 1.8 mg/day (by 8.0% and 11.9%, respectively, $p < 0.01$ for each) but not with the initial dose of 0.6 mg/day (Table 2).

For HbA1c, a significant decrease from baseline was noted with liraglutide doses of 1.2 mg/day and 1.8 mg/day (by 20.0 and 26.5%, respectively, $p < 0.01$) but not with the initial dose of 0.6 mg/day (Table 2).

For FPG (by 33.4%, 34.2%, and 49.5% reduction at 0.6-mg, 1.2-mg, and 1.8-mg doses, respectively, p ranged < 0.001 to < 0.01) and PPG (by 24.5%, 28.0%, and 39.3% reduction at 0.6-mg, 1.2-mg, and 1.8-mg doses, respectively, p ranged < 0.001 to < 0.01), a significant reduction from baseline was evident for all doses of liraglutide starting from the initial dose of 0.6 mg/day (Table 2).

When the change from the 1.2 mg/day dose to the 1.8 mg/day dose was evaluated, all glycemic parameters showed a significant reduction ($p < 0.01$ for each), whereas no further reduction was noted in body weight (Table 2).

Table 1 Baseline characteristics

	Baseline characteristics
Age (year), mean (SD, min–max)	48 (19, 32–68)
Gender, *n* (%)	
Female	13 (48.1)
Male	14 (51.9)
Body weight (kg), mean (SD, min–max)	113.9 (26.6, 80–180)
Duration of diabetes, *n* (%)	
< 5 years	14 (51.9)
5–10 years	8 (29.6)
> 10 years	5 (18.5)
HbA1c (%), mean (SD, min–max)	9.8 (1.9, 7.5–14.0)
FPG (mg/dL), mean (SD, min–max)	251.6 (89.0, 110.0–421.0)
PPG (mg/dL), mean (SD, min–max)	282.0 (92.0, 147.0–520.0)

FPG fasting plasma glucose, *PPG* postprandial glucose

Discussion

Our findings indicate significantly improved HbA1c, FPG, and PPG values as well as a significant reduction in body weight after the implementation of once-daily liraglutide as an add-on to OAD therapy in obese patients with inadequately controlled T2D. Our findings emphasize the efficacy of liraglutide on weight loss and HbA1c reduction only after the patients were titrated to a 1.2-mg daily dose and that there was no further reduction in body weight but continued improvement in glycemic parameters when patients were uptitrated to the highest daily liraglutide dose of 1.8 mg/day.

Data from randomized trials of liraglutide indicate the favorable efficacy and safety profile of liraglutide when used as a monotherapy or as an add-on to other treatments (i.e., metformin, sulfonylurea, thiazolidinedione, and basal insulin) in T2D patients [19–21].

In the current study, once-daily liraglutide improved the HbA1c from 9.8% at baseline to 7.8% at the 1.2-mg dose (reduced by 20.0%) and to 7.2% (reduced by 26.5%) at the 1.8-mg dose treatment periods, each lasting for 3 months. Similarly, in a past study conducted in an Arab population of T2D patients, the authors reported a reduction in HbA1c from 8.3 to 7.7% at the 3rd month and to 7.6% at the 6th month of liraglutide therapy [22]. In a meta-analysis of 9 randomized controlled trials (RCTs) of 2981 patients receiving liraglutide as an add-on to metformin, the authors concluded that there was an association of liraglutide with significantly decreased HbA1c compared with placebo (by − 0.36%), while subgroup analysis revealed a significant reduction in HbA1c at a dose of liraglutide of 1.8 mg/day (by − 0.47%) and 1.2 mg/day (by − 0.35%) but not at a dose of 0.6 mg/day (by − 0.09%) [23]. Our findings also revealed no significant improvement in HbA1c from baseline with a 0.6-mg dose of liraglutide, while the HbA1c reductions obtained by 1.2 mg (by 20.0%) and 1.8 mg (by 26.5%) doses of liraglutide were significant compared with pretreatment values.

Data from the SCALE trial of 846 T2D patients from 9 countries regarding 56-week, once-daily 3.0 mg liraglutide ($n = 423$), 1.8 mg liraglutide ($n = 211$), or placebo ($n = 212$) as an add-on to OADs (metformin, thiazolidinedione, sulfonylurea) revealed significantly higher efficacy of a 3.0-mg vs. a 1.8-mg dose of liraglutide on glucose-related measures, including a reduction in HbA1c and FPG levels and achieving a target HbA1c level of ≤ 6.5% [15]. Similarly, continued improvement in HbA1c, FPG, and PPG parameters was observed with increasing liraglutide doses in our cohort, and the highest glycemic efficacy was achieved after patients were uptitrated to the highest daily liraglutide dose of 1.8 mg.

Table 2 Efficacy of once daily liraglutide treatment in 0.6-mg, 1.2-mg, and 1.8-mg doses on body weight and glycemic parameters

	Pre-treatment visit (Baseline)	Post-treatment visits		
		Month 1 1-month (0.6 mg/day)	Month 4 3-month (1.2 mg/day)	Month 7 3-month (1.8 mg/day)
Body weight (kg)				
Visit value, mean (SD)	113.9 (26.6)	112.8 (27.0)	104.8 (27.5)	100.3 (23.4)
Change from baseline	Absolute (kg); %	1.1; 0.9	9.1; 8.0	13.6; 11.9
	p value	> 0.05	*< 0.01*	*< 0.01*
Change from 1.2 mg/day dose	absolute (kg); %			4.5; 4.3
	p value			0.3
HbA1c (%)				
Visit value, mean (SD)	9.8 (1.9)	8.9 (1.3)	7.8 (1.5)	7.2 (0.7)
Change from baseline	Absolute (%); %	1.0; 10.2	2.0; 20.0	2.6; 26.5
	p value	0.058	*< 0.01*	*< 0.01*
Change from 1.2 mg/day dose	absolute (%); %			0.6; 7.7
	p value			*< 0.01*
FPG (mg/dL)				
Visit value, mean (SD)	251.6 (89.0)	167.9 (53.4)	165.3 (69.7)	127.0 (35.2)
Change from baseline	absolute (mg/dL); %	84; 33.4	85.7; 34.2	124.6; 49.5
	p value	*< 0.001*	*< 0.01*	*< 0.01*
Change from 1.2 mg/day dose	absolute (mg/dL); %			38.3; 23
	p value			*< 0.01*
PPG (mg/dL)				
Visit value, mean (SD)	285.5 (92.0)	215.8 (74.1)	205.4 (66.5)	173.0 (44.5)
Change from baseline	absolute (mg/dL); %	70; 24.5	80.1; 28.0	112.3; 39.3
	p value	*< 0.001*	*< 0.01*	*< 0.01*
Change from 1.2 mg/day dose	absolute (mg/dL); %			32.3; 15.7
	p value			*< 0.01*

Values in italic indicate statistical significance ($p < 0.05$)

FPG fasting plasma glucose, *PPG* postprandial glucose

Indeed, the superiority of liraglutide 1.8 mg/day over placebo in improving glycemic control was also reported by the LIRA-ADD2SGLT2i trial in T2D patients with inadequately controlled HbA1c despite treatment with sodium-glucose co-transporter-2 (SGLT2) inhibitors with or without metformin [24]. The authors also noted the glycemic efficacy of liraglutide in T2D patients to be clinically important given the achievement of a target of HbA1c < 7.0% and ≤ 6.5% by more than half and one-third of patients, respectively, as well as the maintenance of good glycemic control without severe hypoglycemia or weight gain in half of patients [24]. The PIONEER-4 trial compared oral semaglutide (dose escalated to 14 mg), liraglutide (dose escalated to 1.8 mg), or placebo in T2D patients, and the findings in the liraglutide arm included a mean − 1.1% change from baseline in HbA1c and − 3.1 kg weight loss at week 26 [25]. In the SUSTAIN 10 trial, which aimed to reflect real-world clinical practice by comparing the most commonly prescribed doses for once-daily liraglutide (1.2 mg) vs. once-weekly semaglutide (1.0 mg) in Europe, 30-week liraglutide therapy in patients with T2D uncontrolled by 1–3 OADs was reported to reduce mean HbA1c (baseline 8.2%) by 1.0% and mean body weight (baseline 96.9 kg) by 1.9 kg, while semaglutide was superior to liraglutide in improving glycemic control and reducing body weight [26].

Our findings revealed significant reductions in FPG (85 mg/dL (4.7 mmol/L), 84.7 mg/dL (4.8 mmol/L), and 124.6 mg/dL (6.9 mmol/L), respectively) and PPG (70 mg/dL (3.9 mmol/L), 80.1 mg/dL (4.4 mmol/L), and 112.3 mg/dL (6.2 mmol/L), respectively) with 0.6-, 1.2-, and 1.8-mg doses of liraglutide. This seems to indicate the achievement of a more favorable glycemic efficacy with liraglutide in our cohort compared with the LEAD-2 trial, which revealed lower decreases from baseline in FPG (1.1 mmol/L, − 1.6 mmol/L, and − 1.7 mmol/L) and in PPG (− 1.7 mmol/L, − 2.3 mmol/L, and − 2.6 mmol/L) for 0.6 mg, 1.2 mg, and 1.8 mg liraglutide, respectively [27]. This seems notable given that long-acting GLP-1RAs are considered to be noninsulin injectable agents that target both FPG and PPG and, therefore, to show a greater

HbA1c reduction with no risk of hypoglycemia and the additional benefit of weight loss [12, 13, 16, 17].

In a model-based meta-analysis of 76 publications on the glycemic efficacy of 90-day DPP-4i, GLP-1RA, and SGLT2i as add-on treatments to metformin monotherapy in T2D patients, long-acting GLP-1RAs including liraglutide (FPG reduction by − 22.1% and HbA1c reduction by − 16.3%) were concluded to provide better glycemic control [28]. In fact, given that liraglutide was used as an add-on to either metformin alone or metformin plus insulin secretagogues (i.e., DPP-4 inhibitors and sulfonylureas) in our cohort, it should also be noted that higher efficacy of liraglutide has been suggested when used as an add-on to metformin alone than when used as an add-on to insulin secretagogues, particularly in reducing cardiovascular risk in T2D patients [29].

Data from the meta-analysis of 9 RCTs with 2981 patients receiving liraglutide as an add-on to metformin revealed that liraglutide lowered body weight more than the placebo (by − 2.13 kg), while subgroup analysis revealed significantly reduced body weight at all three dosages, including 1.8 mg/day (by − 2.07 kg), 1.2 mg/day (by − 2.21 kg), and 0.6 mg/day (by − 1.90 kg) [23]. Data from a meta-analysis of 5 RCTs involving 1440 T2D patients revealed significantly lower HbA1c with 1.2 mg (by 0.31%) and 1.8 mg (by 0.38%) liraglutide than with sitagliptin as an add-on to metformin, while only the 1.8 mg liraglutide group had significant body weight loss (by − 1.12%) [30]. Data from the SCALE trial of 846 T2D patients from 9 countries comparing 56-week, once-daily 3.0 mg liraglutide ($n = 423$), 1.8 mg liraglutide ($n = 211$) and placebo ($n = 212$) as an add-on therapy to 0–3 OADs (metformin, thiazolidinedione, sulfonylurea) revealed significantly higher weight loss with 3.0 mg liraglutide (6.0%, 6.4 kg) than with 1.8 mg liraglutide (4.7%, 5.0 kg) or placebo (2.0%, 2.2 kg) [15].

In the current study, only 1.2 mg (by − 9.1 kg, 8%) and 1.8 mg (by − 13.6 kg, 11.9%) doses of liraglutide were associated with significant weight loss when compared with baseline, and no further reduction in body weight was noted when the dose was titrated from 1.2 to 1.8 mg. Past studies indicated an association of a 1.8-mg dose of liraglutide with a 4–6-kg reduction in body weight and a greater proportion of patients achieving a 5–10% loss of weight with liraglutide than with placebo [31], while liraglutide versus placebo was also reported to reduce body weight by 4.8 kg, 5.5 kg, 6.3 kg, and 7.2 kg for doses of 1.2 mg, 1.8 mg, 2.8 mg, and 3 mg, respectively [32]. A similar trend of liraglutide-dependent weight loss from baseline to the 3rd month and 6th month of therapy was also reported in a past study in an Arabic T2D population (from 96.0 to 94.8 kg and to 94.5 kg, respectively) [22].

The amount of weight loss obtained via 1.2-mg and 1.8-mg doses of once-daily liraglutide in our obese T2D patients seems much higher than those reported by other studies in T2D patients. This may be attributed to the fact that the T2D patients enrolled in the current study were highly motivated to lose weight and keen to adhere to lifestyle interventions, and their socioeconomic status was favorable enough to afford out-of-pocket expenses.

In fact, poor glycemic control in younger age groups of diabetes patients has been considered to be associated with lower adherence to a diabetes care plan and lifestyle changes due to the active occupational and social life in this age group [33, 34]. In this regard, given the relatively young age of our patients, with at least half of them having suffering from diabetes only for less than 5 years, the efficacy of liraglutide in our study population also seems to indicate the likelihood of obesity rather than early-stage diabetes (with no as-yet apparent diabetes-related complications) to be considered a major complaint by patients, leading to the adoption of a better self-care practice towards improved adherence to lifestyle interventions. Another important factor to be considered is the achievement of favorable outcomes in our T2D patients despite challenging circumstances due to vast destruction of the Iraqi health system infrastructure after the 2003 War, resulting in the restrictions in the provision of essential care [35] and poor practice of daily diabetes self-management protocols with strong adverse impact of stressful life factors (i.e., a lack of clean water and electricity and political instability) and the unavailability of educational programs in Iraq [36, 37].

In addition, it should be noted that higher doses of liraglutide (3.0 mg vs. 1.8 mg) were reported to be associated with better scores of weight-related quality of life along with a significant improvement in participants' physical function, while improvements in quality of life and treatment satisfaction are suggested to reinforce desired behavior via better adherence to treatment and lifestyle interventions [15]. Moreover, for the same degree of weight loss, liraglutide treatment was also reported to be associated with a greater improvement in β-cell function and more remarkable reduction in visceral fat than a standardized lifestyle intervention protocol in T2D patients [38, 39].

Certain limitations to this study should be considered. First, due to the retrospective single-center design of the present study, establishing causality between the drug and the observed effects is not possible. Second, the lack of data on certain patient-reported outcome measures related to quality of life or treatment satisfaction is another limitation, which would otherwise extend the knowledge achieved in the current study.

In conclusion, our findings indicate favorable efficacy of liraglutide as an add-on to metformin-based OADs in weight reduction and improved glycemic parameters, including HbA1c, FPG, and PPG, in obese patients with inadequately controlled T2D. Once-daily liraglutide treatment was associated with significant weight loss and improved HbA1c levels only at 1.2-mg and 1.8-mg doses, while a 1.8-mg dose compared with a 1.2-mg dose seems to enable a further

improvement in glycemic control but not in weight loss. Accordingly, our findings support the utility of once-daily liraglutide as an add-on to OADs as an effective option to promote weight loss along with glycemic control in obese T2D patients and emphasize the likelihood of higher doses to enable better glycemic control with similar weight loss.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethics approval While the present study was exempt from the requirements of ethical approval because of its retrospective design, the study was conducted in full accordance with local Good Clinical Practice guidelines and current legislation, and permission was obtained from our institutional ethics committee for the use of patient data for publication purposes.

Consent to participate This is a retrospective study.

Consent for publication Permission was obtained from our institutional ethics committee for the use of patient data for publication purposes.

References

1. Mauricio D, Meneghini L, Seufert J, Liao L, Wang H, Tong L, et al. Glycaemic control and hypoglycaemia burden in patients with type 2 diabetes initiating basal insulin in Europe and the USA. Diabetes Obes Metab. 2017;19:1155–64.
2. Al-Rasheedi AA. Glycemic control among patients with type 2 diabetes mellitus in countries of Arabic Gulf. Int J Health Sci (Qassim). 2015;9:345–50.
3. Alramadan MJ, Magliano DJ, Almigbal TH, Batais MA, Afroz A, Alramadhan HJ, et al. Glycaemic control for people with type 2 diabetes in Saudi Arabia—an urgent need for a review of management plan. BMC Endocr Disord. 2018;18:62.
4. Esteghamati A, Larijani B, Aghajani MH, Ghaemi F, Kermanchi J, Shahrami A, et al. Diabetes in Iran: prospective analysis from first Nationwide diabetes report of National Program for Prevention and Control of Diabetes (NPPCD-2016). Sci Rep. 2017;7:13461.
5. Mansour AA. Patients' opinion on the barriers to diabetes control in areas of conflicts: the Iraqi example. Confl Health. 2008;2:7.
6. Al-Timimi DJ, Ali AF. Serum 25(OH) D in diabetes mellitus type 2: relation to glycaemic control. J Clin Diagn Res. 2013;7:2686–8.
7. Saeed H, Haj S, Qasim B. Estimation of magnesium level in type 2 diabetes mellitus and its correlation with HbA1c level. Endocrinol Diabetes Metab. 2018;2:e00048.
8. International Diabetes Federation. IDF Diabetes Atlas. 9th ed. Brussels: International Diabetes Federation; 2019. https://www.diabetesatlas.org/en/
9. Mansour AA, Al DF. Diabetes in Iraq: facing the epidemic. A systematic review. Wulfenia. 2015;22:258–78.
10. Nauck MA, Meier JJ. The incretin effect in healthy individuals and those with type 2 diabetes: physiology, pathophysiology, and response to therapeutic interventions. Lancet Diabetes Endocrinol. 2016;4:525–36.
11. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet. 2006;368:1696–705.
12. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in Diabetes - 2019. Diabetes Care. 2019;42(Suppl. 1):S90–102.
13. Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, et al. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2018;61:2461–98.
14. Victoza [package insert]. Plainsboro, NJ: Novo Nordisk Inc; 2017.
15. Davies MJ, Bergenstal R, Bode B, Kushner RF, Lewin A, Skjøth TV, et al. NN8022-1922 study group. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE diabetes randomized clinical trial. JAMA. 2015;314:687–99.
16. Howell R, Wright AM, Clements JN. Clinical potential of liraglutide in cardiovascular risk reduction in patients with type 2 diabetes: evidence to date. Diabetes Metab Syndr Obes. 2019;12:505–12.
17. Garber AJ. Long-acting glucagon-like peptide 1 receptor agonists: a review of their efficacy and tolerability. Diabetes Care. 2011;34(Suppl. 2):S279–84.
18. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. LEADER steering committee; LEADER trial investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375:311–22.
19. 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;32:1224–30.
20. Russell-Jones D, Vaag A, Schmitz O, Sethi BK, Lalic N, Antic S, et al. Liraglutide Effect and Action in Diabetes 5 (LEAD-5) met+SU Study Group. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomized controlled trial. Diabetologia. 2009;52:2046–55.
21. Buse JB, Rosenstock J, Sesti G, Schmidt WE, Montanya E, Brett JH, et al. 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.
22. Bashier AMK, Bin Hussain AAK, Abdelgadir EIE, Eltinay AT, Thadani P, Abdalla ME, et al. Liraglutide effect in reducing HbA1c and weight in Arab population with type2 diabetes, a prospective observational trial. J Diabetes Metab Disord. 2015;14:48.
23. Gu J, Meng X, Guo Y, Wang L, Zheng H, Liu Y, et al. The efficacy and safety of liraglutide added to metformin in patients with diabetes: a meta-analysis of randomized controlled trials. Sci Rep. 2016;6:32714.
24. Blonde L, Belousova L, Fainberg U, Garcia-Hernandez PA, Jain SM, Kaltoft MS, et al. Liraglutide as ADD-on to sodium-glucose co-transporter-2 inhibitors in patients with inadequately controlled type 2 diabetes: LIRA-ADD2SGLT2i, a 26-week, randomized, double-blind, Placebo-Controlled Trial. Diabetes Obes Metab. 2020;22:929–37.
25. Pratley R, Amod A, Hoff ST, Kadowaki T, Lingvay I, Nauck M. Et al; PIONEER 4 investigators. Oral semaglutide versus

subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial. Lancet. 2019;394: 39–50.
26. Capehorn MS, Catarig AM, Furberg JK, Janez A, Price HC, Tadayon S, et al. Efficacy and safety of once-weekly semaglutide 1.0mg vs once-daily Liraglutide 1.2mg as add-on to 1-3 Oral antidiabetic drugs in subjects with type 2 diabetes (SUSTAIN 10). Diabetes Metab. 2020;46:100–9.
27. Nauck M, Frid A, Hermansen K, Shah NS, Tankova T, Mitha IH, 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.
28. Inoue H, Tamaki Y, Kashihara Y, Muraki S, Kakara M, Hirota T, et al. Efficacy of DPP-4 inhibitors, GLP-1 analogues, and SGLT2 inhibitors as add-ons to metformin monotherapy in T2DM patients: a model-based meta-analysis. Br J Clin Pharmacol. 2019;85:393–402.
29. Ciresi A, Vigneri E, Radellini S, Pantò F, Giordano C. Liraglutide improves cardiovascular risk as an add-on to metformin and not to insulin secretagogues in type 2 diabetic patients: a real-life 48-month retrospective study. Diabetes Ther. 2018;9:363–71.
30. Li M, Yang Y, Jiang D, Ying M, Wang Y, Zhao R. Efficacy and safety of liraglutide versus sitagliptin both in combination with metformin in patients with type 2 diabetes: a systematic review and meta-analysis. Medicine (Baltimore). 2017;96:e8161.
31. Mehta A, Marso SP, Neeland IJ. Liraglutide for weight management: a critical review of the evidence. Obes Sci Pract. 2017;3:3–14.
32. Jelsing J, Vrang N, Hansen G, Raun K, Tang-Christensen M, Knudsen LB. Liraglutide: short-lived effect on gastric emptying—long lasting effects on body weight. Diabetes Obes Metab. 2012;14:531–8.
33. Alramadan MJ, Afroz A, Hussain SM, Batais MA, Almigbal TH, Al-Humrani HA, et al. Patient-related determinants of glycaemic control in people with type 2 diabetes in the Gulf cooperation council countries: a systematic review. J Diabet Res. 2018;2018: 9389265.
34. Sanal TS, Nair NS, Adhikari P. Factors associated with poor control of type 2 diabetes mellitus: a systematic review and meta-analysis. J Diabetol. 2011;3:1–10.
35. Hussain AM, Lafta RK. Burden of non-communicable diseases in Iraq after the 2003 war. Saudi Med J. 2019;40:72–8.
36. Mikhael EM, Hassali MA, Hussain SA, Shawky N. Self-management knowledge and practice of type 2 diabetes mellitus patients in Baghdad, Iraq: a qualitative study. Diabetes Metab Syndr Obes. 2018;12:1–17.
37. Alzubaidi H, Mc Namara K, Browning C, Marriott J. Barriers and enablers to healthcare access and use among Arabic-speaking and Caucasian English-speaking patients with type 2 diabetes mellitus: a qualitative comparative study. BMJ Open. 2015;5:e008687.
38. Færch K, Johansen NB, WitteDR LT, Jørgensen ME, Vistisen D. Relationship between insulin resistance and b-cell dysfunction in subphenotypes of prediabetes and type 2 diabetes. J Clin Endocrinol Metab. 2015;100:707–16.
39. Santilli F, Simeone PG, Guagnano MT, Leo M, Maccarone MT, Di Castelnuovo A, et al. Effects of liraglutide on weight loss, fat distribution, and β-cell function in obese subjects with Prediabetes or early type 2 diabetes. Diabetes Care. 2017;40:1556–64.