Original Article

Effects of liraglutide addition to multiple diabetes regimens on weight and risk of hypoglycemia for a cohort with type 2 diabetes followed in primary care clinics in Saudi Arabia

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Abstract

Context: Available therapies for type 2 diabetes mellitus (T2DM) do not adequately control glycemia in the long term as they do not address the issue of declining beta cell function and do not impact positively on weight or cardiovascular concerns associated with the disease. **Aims:** To measure changes in hemoglobin A1c, weight, and hypoglycemia after the addition of liraglutide to 3 therapeutic regimens of patients with T2DM. **Settings and Design:** An observational cohort study that was implemented in Al-Wazarat Health Center in Riyadh, Saudi Arabia. **Methods and Materials:** The study included 38 T2DM patients who were screened for initiation of liraglutide in combination with their treatment regimens; sulphonylurea, sulphonylurea with basal insulin (glargine), and multiple daily injections of insulin. The cohort was followed for 12 months, and the liraglutide was started with 0.6 mg dose that escalated to 1.2 and 1.8 mg. Glycemic level and weight were measured 3 times, whereas hypoglycemia was measured 2 times. **Statistical Analysis Used:** Quantitative continuous paired data were compared using a paired *t*-test and the nonparametric Wilcoxon signed rank test. **Results:** There was a statistically significant reduction of hemoglobin A1c with 1.2 mg dose (mean difference = 0.84%, $P = 0.003$). There were no statistically significant differences regarding the effect of liraglutide in addition to the 3 treatment regimens on patients' weight ($P = 0.08, 0.472, 0.08$, respectively). Regarding hypoglycemia, liraglutide has showed minimal effect. **Conclusions:** Sustained effect of liraglutide on glycemic control in patients with T2DM without any major hypoglycemic episodes.

Keywords: Glycemic control, hypoglycemia, liraglutide, type 2 diabetes mellitus, weight

Introduction

Type 2 diabetes mellitus (T2DM) is a progressive multisystem disease in which individuals exhibit varying degrees of declining beta cell function, insulin resistance, and a failure to suppress postprandial glucagon secretion. Currently, available therapies do not adequately control glycemia in the long term as they do not address the issue of declining beta cell function and do not impact positively on weight or cardiovascular concerns associated with the disease such as edema and weight gain.[1]

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Literature Review

T2DM therapies often comprise complex treatment and titration regimens and can increase the risk of hypoglycemia

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and undesirable effects.[2-4] Glucagon-like peptide-1 (GLP-1) is a naturally occurring incretin hormone with a wide range of physiological actions that make it a potent blood-glucose-lowering agent with the potential to modify the natural history of T2DM. Currently, liraglutide has been shown to have a positive impact on cardiovascular outcomes and other benefits.[5,6] Treatment with liraglutide produced substantial and clinically significant reductions in hemoglobin A1c (HbA1c), and fasting and postprandial glucose levels, with a low risk of hypoglycemia, and moderate weight loss.[2,7-10] Also, liraglutide treatment alone or in combination with oral antidiabetic agents demonstrated significantly larger HbA1c reductions compared with glimepiride (monotherapy),[10] rosiglitazone (in combination with sulfonylurea),[8] and insulin glargine (in combination with metformin plus sulfonylurea).[7] Endogenous GLP-1 suppresses appetite and energy intake in both normal weight and obese individuals.[11] As monotherapy, liraglutide lowered HbA1c from the mean baseline value (8.2%) by 0.84% and by 1.14% with 1.2 and 1.8 mg doses, respectively, compared with a 0.51% reduction with glimepiride 8 mg.[7,9,10,12,13] The LEAD trials showed a decrease in mean weight ranging from 1 to 3.2 kg (2.2–7.04 pounds) over the course of 26 or 52 weeks with liraglutide except in the LEAD-1 study.[7,9,10,12,13] The reduction was more statistically significant for liraglutide than for the comparative treatments. In LEAD-1, when glimepiride was combined with liraglutide, a reduction in body weight was observed with liraglutide 1.8 mg and placebo. Weight loss in both groups was <0.5 kg (1 pound).[8]

The aim of this study is to measure changes in HbA1c, weight, and risk of hypoglycemia (mild, moderate, and severe) because of addition of liraglutide to sulphonylurea, sulphonylurea with basal insulin, or multiple daily injections (MDI) of insulin in obese insulin-resistant patients with T2DM during the study period.

Subjects and Methods

Setting

The study was conducted in Al-Wazarat Health Center (WHC), which is the largest family medicine center in Riyadh, Saudi Arabia. The yearly total number of diabetic patients followed in WHC is ~13,000 patients. They are served by family medicine clinics dedicated for chronic diseases (6 morning and 5 afternoon clinics) which are run by family physicians, a clinical pharmacy clinic (covers 10 sessions per week), diabetic educator, health educator, dietitian, and a social worker. The current data were collected from the clinical pharmacy clinic.

Study design

An observational cohort design of all diabetic patients with age 18–75 years followed in chronic diseases center at family and community medicine department in Prince Sultan Military Medical City. Subjects were screened and enrolled if they meet the inclusion criteria for adding liraglutide to their therapeutic diabetic regimen.

Patient population

Inclusion criteria included any T2DM patient treated with sulphonylurea as monotherapy for a period ≥3 months, sulphonylurea with basal insulin (glargine) during the previous 3 months, or MDI for a period ≥3 months, 18–75 years of age, HbA1c 7%–14%, and body mass index (BMI) ≥30.

Exclusion criteria included impaired renal function, impaired hepatic function (liver enzymes ≥3 times upper normal limit), plasma creatinine >130 μmol/L, diabetic gastroparesis, heart failure (left ejection fraction >30), history of pancreatitis, family history of thyroid cancer, and using any drug that could interfere with glycemic blood level other than metformin or sulphonylurea.

As per good clinical practice guidelines regarding management of diabetes, all diabetic patients starting liraglutide will be screened for agreed criteria for using liraglutide including absence of family history of thyroid cancer, BMI >30, absence of arrhythmia or high heart rate (>90), taking sulphonylurea, sulphonylurea with basal insulin (glargine), or MDI of insulin with inadequate control of blood sugar, and documented weight gain.

Safety variables included adverse events, vital signs, ECG, biochemical and hematology measures, and subject-reported hypoglycemic episodes. The later variable encompassed the number of hypoglycemia events per hypoglycemia category that were reported through self-monitoring of blood glucose (mild hypoglycemia: glycemic blood level <70 mg/dL, an urgent need to eat, and shakiness perspiration; moderate hypoglycemia: glycemic blood level <55 mg/dL, dizziness, sleepiness confusion, difficulty speaking, and feeling anxious or weak; severe hypoglycemia: glycemic blood level <35–40 mg/dL, seizure or convulsion, loss of consciousness, coma, and third-party assistance or medical intervention).

Sample size calculation

Convenience sample that included all obese diabetic patients who meet the inclusion criteria.

Data collection

Thirty-eight diabetic patients who met the inclusion criteria and agreed to participate in the study were included in the study. Demographic and clinical data included age, gender, duration of diabetes and date of starting liraglutide, the liraglutide dose at the beginning and at the end of the study after titration, and the treatment group. There were 3 treatment groups; group 1 included 6 patients on sulphonylurea, group 2 included 9 patients on sulphonylurea and basal insulin, and group 3 included 23 patients on MDI of insulin.

The cohort was followed for 12 months and liraglutide starting dose was 0.6 mg that escalated to 1.2 and 1.8 mg based on patient tolerance. The glycemic level and weight were measured at baseline and 2 follow-up visits throughout the 12 months. The self-reported blood glucose readings were recorded twice

during the period of the study including before breakfast, after breakfast, after lunch, and after dinner periods each time to detect hypoglycemia which was categorized into 4 groups: no hypoglycemia, mild hypoglycemia, moderate hypoglycemia, and severe hypoglycemia.

Statistical methods

Data entry and statistical analysis were done using Microsoft Excel 2016 and SPSS 20.0 statistical software packages. Data were presented using descriptive statistics in the form of frequencies and percentages for qualitative variables, and means, standard deviations, and medians for quantitative variables. Quantitative continuous paired data were compared using a paired *t*-test and the nonparametric Wilcoxon signed rank test. Statistical significance was considered at *P* value <0.05.

Ethical considerations

The approval for this study was taken from the research ethics committee at the Prince Sultan Military Medical City (registration no.: HAP-01-R-079). Informed consent was obtained from each participant after a full explanation of the study. Participant's confidentiality was maintained throughout the study, and his/her information was not used for other purposes other than this study.

Results

The study enrolled 38 patients with T2DM. Table 1 illustrates the demographic characteristics of the participants. It shows that the participants included 17 males (44.7%) and 21 females (55.3%), with a mean age of 50.6 ± 10.8 years.

Table 2 illustrates the clinical characteristics of the participants. It shows that the mean duration of T2DM was 13.5 ± 7.4 years, whereas the mean duration of using liraglutide was 11.3 ± 1.4 months. According to their treatment regimens, participants were divided into 3 groups: the sulphonylurea treatment group which included 6 patients; the sulphonylurea and basal insulin group which included 9 patients; and finally, the MDI group which included 23 patients. Regarding hypoglycemia, there was only 1 mild case at the baseline "Before Breakfast" period as shown in Table 2. In addition to this case, there were only 5 cases of hypoglycemia throughout the whole 8 times of measuring blood sugar; 1 mild case and 1 moderate case during the follow-up "before breakfast" period, 1 moderate case during the baseline "after lunch" period, 1 mild case during the baseline "after dinner" period, and 1 mild case during the follow up "after dinner" period.

Table 3 shows the results of measuring the study variables during the baseline period and the 2 follow-up periods. It shows that the HbA1c levels have declined in all groups; from 8.3 ± 0.8% to 7.7 ± 0.7% in group 1, from 8.8 ± 1.6% to 8.3 ± 1.4% in group 2, and from 9.0 ± 1.5% to 8.4 ± 1.6% in group 3. However, this decline in HbA1c levels was not statistically significant [see Table 3].

Table 1: Demographic characteristics of participants in the study sample

Characteristic	Frequency	Percent
Age (years)		
<40	6	15.8
40-<60	22	57.9
60+	10	26.3
Range	25.0-70.0	
Mean±SD	50.6±10.8	
Median	50	
Gender		
Male	17	44.7
Female	21	55.3

Table 2: Clinical characteristics of participants in the study sample

Characteristics	Frequency	Percent
Duration of diabetes mellitus (years)		
<10	11	28.9
10-<20	15	39.5
20+	12	31.6
Range	2.0-30.0	
Mean±SD	13.5±7.4	
Median	11	
HbA1c baseline level (%)		
<9	21	55.3
9-<12	16	42.1
12+	1	2.6
Range	6.3-12.2	
Mean±SD	8.8±1.4	
Median	8.65	
Duration of using liragulitde (months)		
Mean±SD	11.3±1.4	
Treatment groups		
Group 1: sulphonylurea	6	15.8
Group 2: sulphonylurea+basal insulin	9	23.7
Group 3: MDI	23	60.5
First before breakfast blood sugar levels (mg/dL) (mean±SD)		
Group 1: sulphonylurea	96.2±27.0	
Group 2: sulphonylurea+basal insulin	137.3±56.7	
Group 3: MDI	126.4±43.3	
Hypoglycemia categories (before breakfast level)		
No hypoglycemia	37	97.4
Mild hypoglycemia	1	2.6
Moderate hypoglycemia	0	0
Severe hypoglycemia	0	0

MDI: multiple daily injections

Figure 1 illustrates the mean HbA1c levels through the baseline and the 2 follow-up measurements according to 3 treatment groups.

Figure 2 illustrates the mean weight measurements through the baseline and the 2 follow-up measurements according to 3 treatment groups.

Table 4 illustrates the effect of the 3 treatment regimens on HbA1c, weight, and blood sugar. There was no statistically

Table 3: Results of the study variables according to the treatment groups of participants in the study sample through the 3 measurements periods

Variables	Measurements		
	Baseline	First follow-up	Second follow-up
	Mean±SD	Mean±SD	Mean±SD
Group 1: sulphonylurea			
HbA1c (%)	8.3±0.8	8.1±1.1	7.7±0.7
Weight (kg)	100.7±16.7	99.8±18.6	105.7±12.9
SBP (mm Hg)	126.8±17.9	130.0±28.7	130.7±21.5
DPB (mm Hg)	73.5±14.7	74.0±16.4	69.3±13.5
Group 2: sulphonylurea + basal insulin			
HbA1c (%)	8.8±1.6	8.7±1.6	8.3±1.4
Weight (kg)	104.8±27.5	101.8±28.7	104.8±29.4
SBP (mm Hg)	134.7±9.1	131.1±17.4	123.6±8.9
DPB (mm Hg)	75.8±8.2	76.9±12.1	72.8±15.0
Group 3: MDI			
HbA1c (%)	9.0±1.5	8.5±1.3	8.4±1.6
Weight (kg)	103.0±16.4	102.2±17.0	101.3±17.7
SBP (mm Hg)	126.6±13.5	126.9±13.5	123.9±13.4
DPB (mm Hg)	68.4±12.4	66.0±8.7	66.3±13.4

DBP: diastolic blood pressure, MDI: multiple daily injections, SBP: systolic blood pressure

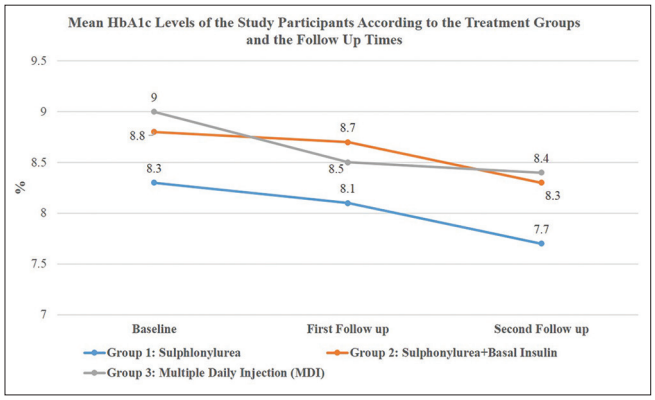

Figure 1: Mean HbA1c levels for study participants throughout the measurement periods

significant difference regarding the effect of the 3 treatment regimens on the HbA1c level (P = 0.254, 0.259, 0.055, respectively). Also, there was no statistically significant difference regarding the effect of the 3 treatment regimens on patients' weight (P = 0.08, 0.472, 0.08, respectively). Finally, there were no statistically significant differences regarding blood sugar measurements for all groups ($P > 0.05$ for all measures).

Table 5 shows the effect of the liraglutide current treatment dose on the HbA1c level. It shows that there was statistically significant difference regarding the effect of the 1.2 mg dose compared with the initial treatment dose (mean difference = 0.84%, $P = 0.003$), whereas there was no statistically significant difference associated with the other 2 doses, namely the 0.6 mg dose and the 1.8 mg dose when compared with the initial treatment dose ($P = 0.363$ and 0.855, respectively). Also, there was no statistically significant difference associated with the 3 liraglutide doses

Table 4: Comparison between the results of the baseline and the follow-up periods of the study variables according to the treatment groups of the participants in the study sample

Variables	Baseline	Last follow-up*	*t*-test	*P*
	Mean±SD	Mean±SD		
Group 1: sulphonylurea				
HbA1c (%)	8.32±0.8	7.68±0.7	1.29	0.254
Weight (kg)	107.6±13.9	105.7±12.9	3.327	0.08
Blood sugar (mg/dL) (before breakfast)	96.2±27.0	106.3±34.9	2.503	0.054
Blood sugar (mg/dL) (after breakfast)	143.0±48.0	158.0±43.6	0.777	0.472
Blood sugar (mg/dL) (After Lunch)	142.6±39.5	153.6±41.1	0.905	0.417
Blood sugar (mg/dL) (after dinner)	176.8±56.0	186.3±35.5	0.502	0.65
Group 2: sulphonylurea + basal insulin				
HbA1c (%)	8.53±1.48	8.28±1.37	1.228	0.259
Weight (kg)	106.4±31.6	104.8±29.4	0.778	0.472
Blood sugar (mg/dL) (before breakfast)	142.9±58.0	136.5±50.7	0.509	0.626
Blood sugar (mg/dL) (after breakfast)	208.8±82.8	183.6±77.1	1.28	0.241
Blood sugar (mg/dL) (after lunch)	188.0±53.1	174.6±55.8	2.250	0.088
Blood sugar (mg/dL) (after dinner)	193.1±80.7	183.1±70.5	0.459	0.662
Group 3: MDI				
HbA1c (%)	9.06±1.53	8.39±1.59	2.042	0.055
Weight (kg)	103.9±17.8	101.3±17.7	1.869	0.08
Blood sugar (mg/dL) (before breakfast)	126.3±49.4	113.7±41.8	1.308	0.209
Blood sugar (mg/dL) (after breakfast)	169.8±75.6	160.4±63.7	0.444	0.665
Blood sugar (mg/dL) (after lunch)	158.5±71.4	158.1±61.8	0.022	0.983
Blood sugar (mg/dL) (after dinner)	169.1±72.4	160.6±74.7	0.582	0.571

*Second follow-up for HbA1c and weight, first follow-up for blood sugar; HbA1c: hemoglobin A1c; MDI: multiple daily injections

regarding their effect on patients' weight (P = 0.14, 0.053, 0.677, respectively).

Discussion

In this observational study, a cohort of 38 diabetic patients with HbA1c (7%–14%) was followed at the chronic diseases center for a duration of 12 months after adding liraglutide with different doses (0.6, 1.2, and 1.8 mg) to their treatment regimens which included sulphonylurea and MDI of insulin and basal Insulin on the top of metformin. The results showed statistically significant improvement in glycemic control with the 1.2 mg dose of liraglutide compared with the initial treatment dose. This was associated with an inconsistent effect on weight, which was statistically not significant, and very few mild and moderate hypoglycemic episodes in obese insulin-resistant patients with T2DM.

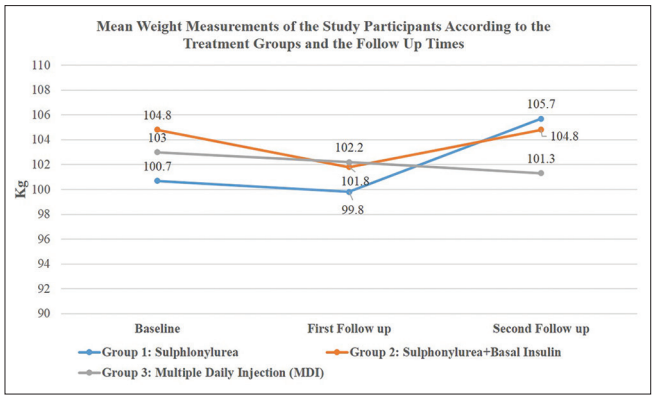

Figure 2: Mean weight for study participants throughout the measurement periods

Prospective studies of the combination of GLP-1 RA plus insulin therapy have shown either superior or equivalent efficacy in glycemic control compared with insulin only.[14-16] Many studies showed that liraglutide produced a substantial and clinically significant reduction in HbA1c and postprandial glucose level, with a low risk of hypoglycemia and moderate weight reduction.[7,9-11] In addition to its effect on glycemic control, liraglutide treatment resulted in significant weight loss compared with placebo (−1.4 kg difference), and a favorable weight difference compared with insulin glargine (−3.4 kg loss).[17] In our study, the results showed that there was no statistically significant difference on patients' weight of the 3 treatment regimens: sulphonylurea, sulphonylurea plus basal insulin, and MDI of insulin, in addition to liraglutide ($P = 0.08$, 0.472, 0.08, respectively). The beneficial effect on weight might be masked or diminished because of associated weight gain with sulphonylurea and insulin, which increases weight by 1.7–4 kg, respectively.[18]

As for the effect of the liraglutide to the current treatment dose on the HbA1c level, there was statistically significant difference regarding the effect of the 1.2 mg dose ($P = 0.003$), whereas there was no statistically significant difference associated with the other 2 doses, namely 0.6 and 1.8 mg dose ($P = 0.363$ and 0.855, respectively).

Flint *et al.'s* study showed no significant difference between fasting and postprandial control between liraglutide and insulin glargine.[11] Similarly, in this study, there was no statistically significant effect of liraglutide on patient home blood monitoring before breakfast and postprandial and this could be explained because of normal blood sugar readings of patients at baseline, so the effect of liraglutide is continuing the normal range of the readings.

The LEADER trial, which was a safety cardiovascular outcome trial that included >9300 patients with a mean follow-up period of 3.5–5 years, has shown that there was a 31% lower rate of severe hypoglycemia and a 20% lower rate of the combination of severe and confirmed hypoglycemia (plasma glucose level <56 mg/dL) in the liraglutide group than in the placebo group.[6] The incidence of hypoglycemia in this study's cases was considered negligible and minimal. There were only 6 cases throughout the whole 8 times of measuring blood sugar; 1 mild case at the first "before breakfast" period, 1 mild case, and 1 moderate case during the second "before breakfast" period, 1 moderate case during the first "after lunch" period, 1 mild case during the first "after dinner" period, and 1 mild case during the second "after dinner" period.

Table 5: Comparison of the study variables according to the current dose of liraglutide used by the participants in the study sample

Variables	Baseline (0.6 mg) Mean±SD	Current dose Mean±SD	*t*-test	*P*
Current dose: 0.6 mg				
HbA1c (%)	9.3±1.9	8.8±1.6	0.973	0.363
Weight (kg)	91.2±15.0	88.2±15.3	1.752	0.14
Current dose: 1.2 mg				
HbA1c (%)	8.7±1.4	7.9±1.4	3.371	0.003*
Weight (kg)	107.2±24.5	103.0±21.6	2.229	0.053
Current dose: 1.8 mg				
HbA1c (%)	8.5±1.0	8.6±1.2	0.191	0.855
Weight (kg)	110.4±15.8	110.9±16.5	Z=0.416**	0.677

*Statistically significant at $P<0.05$. **Wilcoxon signed ranks test; HbA1c: hemoglobin A1c

Strengths and Limitations

This study had strength. The addition of liraglutide to varieties of T2DM treatment regimens considered as a challenge to clinicians to adjust the doses with utilizing the good safety profile and minimal side effects that could be a kind of art in therapeutic T2DM management.

The study had several limitations. First, the relatively small sample size could affect the results' generalizability to some extent. Second, also, not to account there was insulin dose reduction during measurement when combining liraglutide injection with multiple days of insulin in the study. Additionally, the limited time for follow-up as 2 visits throughout the study period did not permit to show the true effect of liraglutide. Furthermore, the combination of liraglutide with sulphonylurea and MDI of insulin that lead to a pronounced effect on weight could decrease the benefit of liraglutide on weight reduction.

Conclusion

This study demonstrated a sustained effect of the liragulitde on glycemic control in obese insulin-resistant patients with T2DM without any major hypoglycemic episodes.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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