

Safety and Efficacy of Liraglutide as an Add-On Therapy to Pre-Existing Anti-Diabetic Regimens during Ramadan, A Prospective Observational Trial

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Abstract

Background: During Ramadan, Muslims fast for prolonged periods, which might predispose patients with diabetes to an increased risk of hypoglycemia. Liraglutide is an incretin that has been associated with reduced risk of hypoglycemia.

Objective: We aimed to assess the safety and efficacy of liraglutide as an add-on therapy to existing anti-diabetic agents during Ramadan.

Patients and methods: Arab patients prescribed liraglutide within the 6 weeks before Ramadan 2014 were recruited to the study. Demographic information and HbA1c levels were recorded at baseline and again within 4 weeks after Ramadan. A telephone call was made to check the frequencies of hypoglycemia during Ramadan.

Results: Of the total of 111 participants, 76 (68.5%) of the participants were female. The mean age was 52.6 ± 10.1. Seventy-seven percent of the patients were aged between 40-60 years. Eighteen patients (16.2%) developed hypoglycemia during Ramadan. None of them required assistance by medical personnel or were admitted to the accident and emergency department. One hundred and five (94.6%) of the participants were on insulin, sulfonylurea or both. Patients who had had diabetes for a longer time had significantly higher frequencies of hypoglycemia during Ramadan (p=0.05).

Conclusion: Adding liraglutide to ongoing anti-diabetic agents did not increase the risk of hypoglycemia. Furthermore, hypoglycemic events were directly related to the duration of diabetes; the longer the duration of diabetes, the more hypoglycemic events the patient had.

Keywords: Liraglutide; Ramadan; Hypoglycemia; Type 2 diabetes; Antidiabetic; Insulin; Arab

Introduction

The prevalence of type2 diabetes is very high in the Gulf region. In 2013, the International Diabetes Federation estimated a prevalence of 23.9% in Saudi Arabia, 23.1% in Kuwait, 22.9% in Qatar, 21.8% in Bahrain, and 19% in the UAE [1]. Type2 diabetes is associated with many short- and long-term complications. One of the most common complications is hypoglycemia, which has been shown in many studies to be associated with increased cardiovascular mortality [2].

Prolonged fasting is one of the main factors associated with increased hypoglycemia and is usually seen in sick patients who are unable to eat or those undergoing a procedure that mandates prolonged fasting. Muslims also practice prolonged fasting during the holy month of Ramadan, which is considered one of the five main pillars of Islam [3]. During this month, Muslims abstain (the literal meaning of the word 'sawm' in Islamic law) from eating and drinking, smoking and consuming oral medications from dawn to dusk [4]. The period of fasting might reach 19 hours in some areas of the world during summer time. Despite the fact that the Quran exempts the sick

from the duty of fasting, many patients with diabetes feel the spiritual need to do so, often against the advice of their health care providers.

The risk of hypoglycemia, dehydration and even hyperglycemia increases dramatically during the month of Ramadan. Data from the Epidemiology of Diabetes and Ramadan (EPIDIAR) study showed that the risk of severe hypoglycemia increased 4.7-fold in type 1 diabetes (3-14 events/100 persons/month) and 7.5-fold in type 2 diabetes (0.4-3.0 events/100 persons/month) [2].

The risk of hyperglycemia is also increased during the month of Ramadan. The EPIDIAR study showed that the risk of severe hyperglycemia is increased 3-fold in type1 diabetes (5-17 events/100 persons/month), and 5-fold in patients with type 2 diabetes (1-5 events/100 persons/month) [2].

To reduce the risk of hypoglycemia during the month of Ramadan, patients who wish to undertake fasting should undergo a pre-Ramadan assessment with their physicians. Regular blood glucose checks while fasting should be encouraged and patients should be advised to break their fast if blood glucose levels are lower than 70 mg/dl or higher than 300 mg/dl. It might be wise for patients to try fasting for several days prior to Ramadan in order to assess the potential risk for hypoglycemia and adjust medications accordingly [5].

Incretin-based therapy is known to be associated with a low risk of hypoglycemia. Liraglutide has been shown to reduce the composite end point of reduced risk of hypoglycemia, be associated with weight loss, and cause no hypoglycemic events. There are no other published data on the safety of GLP1 receptor agonists during Ramadan. However, other incretin-based therapies (DPP4 inhibitors) have been evaluated and were shown to significantly reduce the risk of hypoglycemia.

In this study, we aimed to evaluate the safety and efficacy of liraglutide in patients with type2 diabetes who were intending to fast during the month of Ramadan.

Patients and Methods

This study was part of a larger prospective study that evaluated the safety and efficacy of liraglutide in an Arab population.

Aim of the study

This was an observational study that aimed to evaluate the efficacy and safety of liraglutide in an Arab population with type2 diabetes during the month of Ramadan.

Primary end point

The primary end point of the study was to assess the frequency and severity of hypoglycemic events in patients taking liraglutide during the month of Ramadan.

Secondary end point

We planned to assess the change in HbA1c levels before and after Ramadan.

Study design

This was an observational study that was conducted as part of larger trial that evaluated the efficacy of liraglutide in reducing HbA1c levels and weight in an Arab population at Dubai Hospital and at two other centers of the Dubai Health Authority in the United Arab Emirates. The aim of this study was to assess the safety and efficacy of liraglutide during the month of Ramadan. The original study was approved by the institutional review board and was given the reference number (MRC-08/2013_03). As per local recommendations, consent for participation in the study was obtained from all participants in the trial.

The aim of the study was to assess the frequency and severity of hypoglycemic episodes during the month of Ramadan for patients who were prescribed liraglutide within three months before the month of Ramadan.

Patient recruitment

All adult patients with type 2 diabetes aged between 18 and 70 years, who were started on liraglutide in the period from April 2014 to June 21st, 2014 were recruited to the study. The prescription of liraglutide was compliant with the local recommendations; hence, patients with type1 diabetes, patients with severe renal impairment, pregnant women, and those with a history of pancreatitis were not prescribed liraglutide. We also excluded non-Arab patients and those who did not fast for more than two weeks during the month of Ramadan. The dose

of liraglutide started at 0.6 mg once per day subcutaneously and increased after one week to 1.2 mg and after another week to 1.8 mg per day. Those who did not tolerate the 1.2 mg dose were excluded from the study, while those who did not tolerate the 1.8 mg dose were advised to continue with the dose 1.2 mg per day, as these were the two recommended doses in all LEAD trials.

After obtaining informed consent, patients' data including age, sex, and ethnic group, co-morbidities, concurrent medications and HbA1c level were collected. We measured HbA1c levels within six weeks after Ramadan. In addition, we called all patients and obtained information about hypoglycemic events and their severity, education on dose adjustments before Ramadan, and who conducted the education sessions. Moreover, data on admission for any cause and changes in medications during the month were also reported. Changes in pharmacologic therapy for hypertension and dyslipidemia were allowed if they were deemed necessary and were left to the discretion of the treating physician.

Definitions

Patients were considered to have type 2 diabetes if they fulfilled the American Diabetes Association (ADA) criteria for diagnosis of diabetes mellitus (FBG ≥ 126 mg/dl, RBG ≥ 200 mg/dl, or HbA1c ≥ 6.5 %) [10], or if patients were already on anti-diabetic agents. Patients on metformin alone were not considered diabetic unless they fulfilled the ADA criteria, as many young women were on metformin for treatment of other medical problems, e.g., polycystic ovarian syndrome. Hypertension was defined as a systolic blood pressure of ≥ 140 mmHg and/or diastolic blood pressure of ≥ 90 mmHg or being on antihypertensive medications.

Hypoglycemia was defined as a blood glucose level of < 3.9 mmol (70 mg/dl), in accordance with our local recommendation for Ramadan that advises patients to break their fast at this level and urges them to break their fast if their level reaches < 60 mg/dl. Severe hypoglycemia is defined as hypoglycemia requiring hospital admission.

Statistical analysis

We used the SPSS (statistical program for social science version 16) for data analysis. Quantitative variables were described as mean, SD and range, while qualitative variables were described as number and percentage. We used the Chi-square test to compare qualitative variables between groups and the Fisher exact test when the expected value was less than or equal 5.

For quantitative variables, we used unpaired t-tests to compare two independent groups, and the Paired t-test was used to compare quantitative variable in the same group. A Spearman correlation test was used to rank variables positively or inversely.

The differences were not considered significant if $p > 0.05$, considered significant if $p < 0.05$, and considered highly significant when $p < 0.001$.

Results

The total number of patients in the study was 111, of which 68.5% (n=76) were females. The mean age was 52.6 ± 10.1 , and 77% of the patients were aged between 40-60 years. The mean duration of diabetes was 12.2 ± 5 years. Seventeen (15.3%) of the patients had diabetes for less than 5 years, 27 (24.3%) had diabetes for 5-10 years, 30 (27%) had

diabetes for 10-15 years, and 36 (32.4%) had diabetes for more than 15 years (Table 1).

Variables	No.	%
Age		
	4	3.6%
	9	8.1%
41-50	26	23.4%
51-60	51	45.9%
	21	18.9%
	52.6	20-86
Gender		
Female	76	68.5%
Male	35	31.5%
DM duration (yrs)		
10	44	39.6%
10-15	30	27%
>15	37	33.3%
Education on insulin adjustment		
Doctor	47	42.3%
Nurse	12	10.8%
Self	24	21.6%
None	28	25.2%

Table 1: Baseline characteristics

Forty-seven patients (42.3%) were educated by the treating doctor to adjust their hypoglycemic agents before Ramadan, while a diabetes educator educated 10.8% (n=12). The remaining patients were not educated on dose adjustment; however, 21.6% (n=24) did adjust their dose by themselves. The remaining 25.2% (n=28) did not adjust the dose of hypoglycemic agents during Ramadan.

Eighteen patients (16.2%) developed hypoglycemia during Ramadan. None of them required assistance by medical personnel or were admitted to the accident and emergency department. Six patients (35.3% of those who developed hypoglycemia) required assistance by family members at home.

Three patients experienced a single episode of hypoglycemia, three patients experienced two episodes of hypoglycemia, seven experienced three episodes of hypoglycemia, two experienced four episodes, two experienced five episodes, and one patient experienced eight episodes of hypoglycemia. The mean range of blood glucose during hypoglycemic episodes was 60 ±7.6 mg/dl (40-70 mg/dl).

Three patients did not record blood glucose readings during the hypoglycemic episodes (including the patient with eight hypoglycemic events). Of the patients who had two attacks of hypoglycemia, one had the two episodes of hypoglycemia nocturnally. All hypoglycemic episodes occurred afternoon or before Iftar (time to break the fast).

Only six patients (5.4% of all patients) were not on insulin or sulfonylurea. None of these six patients developed hypoglycemia during Ramadan; however, the number of hypoglycemia episodes was not statistically related to the type of medication that was already being used at baseline. Patients with longer durations of diabetes had significantly higher frequencies of hypoglycemia during Ramadan (p=0.05). Although 46.9% of the patients did not receive structured education before Ramadan, hypoglycemic events were not related to education status (Tables 2 and 3).

Variables	Hypoglycemia episodes	
	r	P
Age	0.13	0.17NS
Education	0.006	0.95NS
HbA1c BR	0.01	0.91NS
HbA1c AR	0.002	0.95NS

This table shows no statistically significant correlation between hypoglycemia episodes versus different variables by using Spearman correlation

Table 2: Correlation between hypoglycemia and different variables

Variables	Beta-coefficient	P	Odd's (95%CI)
Bariatric surgery	0.70	0.11	0.6(-0.3-11.5)
Metformin	0.65	0.40	0.5(-0.11-17)
Sulfonylurea	0.03	0.99	0.4(0.2-10.5)
Insulin	0.32	0.87	0.3(-0.4-18.7)
Duration >15yrs	0.04	0.95	0.09(0.2-16)

This table shows no significant correlation of different predictors by enter technique

Table 3: Predictors of hypoglycemia

The mean HbA1c level before Ramadan was 7.4 1.4% (range: 5.1-12%). This percentage was significantly increased to 8.0 1.7 % (range: 4.0-12.5%, p=0.000) after Ramadan (Figure 1).

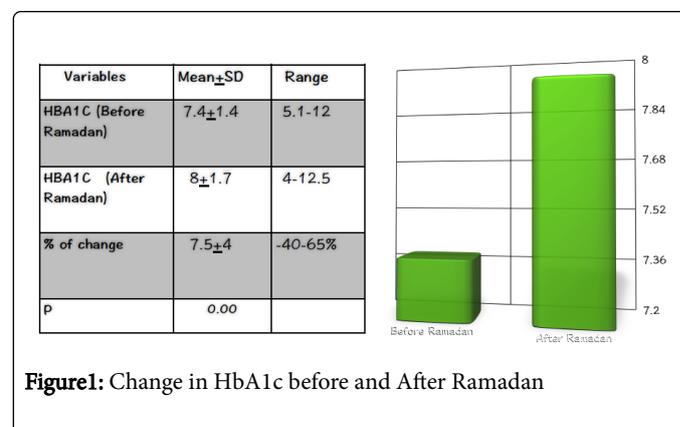


Figure1: Change in HbA1c before and After Ramadan

Discussion

Safety of incretin-based therapy was assessed in many studies that evaluated sitagliptin or vildagliptin versus sulfonylurea as an add-on therapy to metformin during Ramadan. The number of hypoglycemic events with DPP4 inhibitors ranged between zero in the vildagliptin group and 34 (41.7%) in the sulfonylurea group ($p=0.0002$) [6].

In the study titled the effect of vildagliptin relative to sulphonylureas in Muslim patients with type 2 diabetes fasting during Ramadan: the VIRTUE study, there were 36/669 hypoglycemic events in the vildagliptin group (5.4%), which differed significantly from the rate in the sulfonylurea group ($n=123/621$, 19.8%) [OR (95% CI) =0.23 (0.156; 0.340), $p<0.001$] [7]. Another study that compared vildagliptin to sulfonylurea concluded that vildagliptin could safely be used during Ramadan, as it reduces the frequency of hypoglycemic events. Hypoglycemia was recorded in two patients receiving vildagliptin (7.7%) and 16 patients receiving gliclazide (61.5%); the difference between groups was 53.8% [95% confidence interval (CI) 74.9 to 26.3, $p<0.001$] [8].

The safety of sitagliptin was documented in one large trial that randomized 1066 patients to receive either sulfonylurea or sitagliptin. Fewer hypoglycemic episodes were observed with sitagliptin (6.7%) than with sulfonylurea (13.2%) (Mantel-Haenszel relative risk ratio [95% CI]=0.51 [0.34, 0.75]; $p<0.001$) [9].

The only previous study to assess the safety and efficacy of liraglutide during Ramadan was conducted by Brady et al., who randomized patients to either sulfonylurea or liraglutide as an add-on to metformin. The primary outcome was a composite of no severe hypoglycemic events, no weight gain and an HbA1c of $<7\%$, while the secondary outcome was a composite of a weight reduction of 1 kg, no severe hypoglycemic events, and an HbA1c of $<7\%$. The study results reached statistical significance for the secondary outcomes but not for the primary outcome. The authors concluded that liraglutide is safe and effective in reducing weight and HbA1c levels during Ramadan fasting [10].

Our study evaluated the safety of liraglutide when added to an existing anti-diabetic regimen during the month of Ramadan. Ninety-one percent of the patients were on metformin and 94.6% were on either insulin or a sulfonylurea. Our study differs from the previous study in that liraglutide was added on top of an existing regimen and that there was no randomization in our study. Other important differences are the variations in eating habits and life style between patients in the United Kingdom and those in the Middle East during the month of Ramadan. In the Middle East, most people with diabetes loosen their diet, start eating diets with high carbohydrate content, and adopt a less active life style compared to the pre-Ramadan period. This might explain the increase in HbA1c by the end of the Ramadan.

Sulfonylurea safety was assessed in a fewer studies than the number of studies assessing the safety of DPP4 inhibitors. In a trial that included 332 patients, the incidence of hypoglycemic episodes was 3% in newly diagnosed patients and 3.7% in already-treated patients during Ramadan. These figures were similar to those of the pre- and post-Ramadan periods [11]. The finding that patients with newly diagnosed diabetes have a lower risk of hypoglycemia is in keeping with our finding that hypoglycemia is directly related to the duration of diabetes. Aravind et al. conducted a large multicenter observational trial evaluating the risk of hypoglycemia in 1378 subjects with type2 diabetes during Ramadan. Twenty percent of sulfonylurea-treated Muslim subjects with type2 diabetes experienced symptomatic

hypoglycemia while fasting during Ramadan [12]. Relative to the insulin-treated group, hypoglycemia was observed in 14.3% of patients in the glimepiride group, 11.1% of patients in the repaglinide group, and 10% of patients in insulin glargine group. There was no significant difference between the three drug groups regarding the rate of hypoglycemia [13].

In our study, there was no increase in the number of hypoglycemic events when liraglutide treatment was added to treatment with either sulfonylurea or insulin; in fact, none of the patients had a severe hypoglycemic event that required hospital admission. We believe that adding liraglutide to an ongoing anti-diabetic regimen does not result in a significant increase in hypoglycemic events.

In our cohort, a small number of patients developed recurrent hypoglycemic episodes. Most of those patients were the ones who did not receive structured education before Ramadan. The importance of pre-Ramadan structured education was documented in the STEADFAST study, which is a double-blind study that randomized 557 patients with T2DM previously treated with metformin and any sulfonylurea to receive either vildagliptin (50 mg twice daily) or gliclazide plus metformin. The study included four office visits (three pre-Ramadan) and multiple telephone contacts, as well as Ramadan-focused advice. Gliclazide treatment was associated with a lower incidence of hypoglycemia in this study than in the previous observational studies. The results indicated that structured education results in reduced risk of hypoglycemic events during Ramadan [14].

Limitations

The study has many limitations; the most important limitation is that it is a subgroup analysis of a study that was designed to evaluate the effect of liraglutide in reducing HbA1c and weight in Arab population. We recruited patients who attended the clinic before the month of Ramadan. We tried to address all confounding factors including medications, and education, however some confounding factors like exercise could not be assessed.

The main strength of our study is that it is real life scenario as it evaluated liraglutide as add on therapy to pre-existing anti-diabetic agents including Sulphonylureas and insulin. All studies conducted during Ramadan evaluate the study medicine versus SU or another drug. None of the previous studies compared triple therapy or add on to pre-existing insulin.

Conclusion

We conclude that adding liraglutide to an ongoing anti-diabetic regime does not increase the risk of severe hypoglycemia. Furthermore hypoglycemic events were directly related to the duration of diabetes; the longer duration of diabetes, the more hypoglycemic events were observed. Structured education is of paramount importance in reducing the frequency of hypoglycemic episodes. Patients should avoid fasting and maintain a healthier life style during the month of Ramadan to maintain their HbA1c levels.

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