original article

Diabetes, Obesity and Metabolism 16: 527–536, 2014.

ORIGINAL ARTICLE

A randomized controlled trial comparing the GLP-1 receptor agonist liraglutide to a sulphonylurea as add on to metformin in patients with established type 2 diabetes during Ramadan: the Treat 4 Ramadan Trial

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Aims: To compare a sulphonylurea with the glucagon like peptide-1 (GLP-1) receptor agonist liraglutide in combination with metformin in patients on mono/dual oral therapy with established type 2 diabetes fasting during Ramadan.

Methods: Ninety-nine adults intending to fast during Ramadan [50% male, mean age 52 years, body mass index (BMI) 32 kg/m^2] were randomized from two UK sites. Baseline data were collected ≥14 days prior to Ramadan and at 3 and 12 weeks after Ramadan.

Results: At 12 weeks, more patients in the liraglutide compared with the sulphonylurea group achieved a composite endpoint of haemoglobin A1c (HbA1c) < 7%, no weight gain and no severe hypoglycaemia but this did not reach statistical significance [odds ratio (OR) 4.08, 95% confidence interval (CI) 0.97, 17.22, p = 0.06]. From a baseline of 7.7% there was no change in HbA1c at 12 weeks in the sulphonylurea (+0.02%) compared with a 0.3% reduction in the liraglutide group (adjusted coefficient −0.41, 95% CI −0.83, 0.01, p = 0.05). Significant reductions were also observed in weight and diastolic blood pressure (BP) in the liraglutide compared with the sulphonylurea group. Treatment satisfaction was comparable across the treatment groups. There were no episodes of severe hypoglycaemia in either group, however, self-recorded episodes of blood glucose ≤3.9 mmol/l were significantly lower with liraglutide (incidence rate ratio 0.29, 95% CI 0.19, 0.41, p < 0.0001).

Conclusions: Liraglutide compared with sulphonylurea is well tolerated and maybe an effective therapy in combination with metformin during Ramadan with more patients able to achieve target HbA1c, lose or maintain weight with no severe hypoglycaemia. This was achieved with a high level of treatment satisfaction.

Keywords: GLP-1 analogue, randomized trial, type 2 diabetes

Date submitted 15 October 2013; date of first decision 18 November 2013; date of final acceptance 12 December 2013

Introduction

Globally there are more than 1.6 billion Muslims [1]. Most Muslims fast during the month of Ramadan; this involves abstinence from all food and drinks between pre-sunrise and -sunset. Muslims follow the lunar calendar which falls short by 11 days every year compared with the Gregorian calendar hence the month of Ramadan can occur in both summer and winter and this has an effect on the duration of the fast.

The prevalence of diabetes in countries with large Muslim populations is similar to westernized countries, with increases of 10% annually as a result of urbanization and socioeconomic development [2]. Although the Quran exempts 'sick' people from the duty of fasting [3] a study conducted in Muslim populations from 13 countries found that 43% of patients with type 1 diabetes (T1DM) and 79% of people with type 2 diabetes (T2DM) chose to fast [4]. This study reported a 7.5-fold increased risk of severe hypoglycaemia (defined as requiring hospitalization) in those with T2DM who observed Ramadan compared with the preceding months [4]. This is supported by another study which reported the incidence of symptomatic hypoglycaemia to be as high as 20% during Ramadan in those with T2DM taking a sulphonylurea [5].

Following lifestyle modification, people with T2DM often receive metformin as a first line pharmacological therapy for the management of hyperglycaemia. However, the natural history of T2DM means that the majority of patients will require the use of combination antihyperglycaemic agents and for many this will include insulin therapy. The type and/or combination of

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antihyperglycaemic agent(s) will influence the risks associated with fasting and specifically the frequency and severity of hypoglycaemic events. Although many recommendations for the clinical management of diabetes during Ramadan have been published [6–11] there are still a limited number of clinical trials assessing the efficacy and safety of glucose lowering therapies during Ramadan and no consensus about the most appropriate antihyperglycaemic agent(s).

Globally sulphonylureas remain the most common second line glucose lowering therapy predominantly due to their low cost and widespread availability [12,13]. However, the ADA recommends that they are used with caution during Ramadan due to their increased risk of hypoglycaemia [6]. The emergence of new therapies which target the incretin effect, such as the injectable glucagon like peptide-1 (GLP-1) analogues and the oral dipeptidylpeptidase-4 (DPP-4) inhibitors offer alternative therapeutic options. Liraglutide is a GLP-1 receptor agonist administered once daily via subcutaneous injection and has been shown to reduce haemoglobin A1c (HbA1c) levels by up to 1.5% [14], reduce body weight up to 2.8 kg [15] and reduce blood pressure (BP) [16]. Liraglutide is well tolerated [14–19] and provides 24 h glycaemic control by increasing pharmacological plasma levels of GLP-1. Because GLP-1 increases insulin secretion and suppresses glucagon secretion in a glucose-dependent manner liraglutide is associated with low risk of hypoglycaemia [20]. When added to metformin, liraglutide has been shown to be associated with greater glycaemic efficacy, greater weight loss and improved treatment satisfaction compared with the DDP-4 inhibitor sitagliptin [21]. Incretin based therapies are now well established in international guidelines and glucose lowering algorithms [13,22]. GLP-1 analogues are a potential treatment option for patients with T2DM who wish to observe Ramadan and could reduce the risk of hypoglycaemic events, improve glycaemic control and maintain body weight during this period.

The aim of this study is to determine if the addition of liraglutide is more effective in achieving a composite endpoint of HbA1c $< 7.0\%$, no weight gain with no severe hypoglycaemic events, 12 weeks post Ramadan in people with established T2DM compared with a sulphonylurea.

Materials and Methods

Participants

This study was conducted in two UK sites, Leicester and Birmingham, and patients were recruited prior to the month of Ramadan in either 2011 or 2012. Patients were eligible if they were $\geq$18 years with established T2DM on a stable dose of metformin monotherapy or dual therapy of metformin plus a sulphonylurea or pioglitazone with a HbA1c between 6.5 and 12%, and an intention to fast during the holy month of Ramadan for a minimum of 10 consecutive days. Main exclusion criteria were females who were pregnant, breast-feeding or intended to become pregnant, terminal illness, impaired renal function (serum-creatinine $\geq$135 µmol/l for males and $\geq$110 µmol/l for females), impaired liver function [alanine transaminase (ALT) $\geq$2.5 times upper limit of normal], significant active cardiovascular disease including history of myocardial infarction within the past 6 months and/or heart failure [New York Heart Association (NYHA) class III and IV] at the discretion of the investigator, hepatitis B antigen or hepatitis C antibody positive, recurrent major hypoglycaemia as judged by the investigator, severe irritable bowel disorder or previous history of pancreatitis.

Medicines and Healthcare products Regulatory Agency, independent local ethics and Research and Governance approvals were obtained for the study. Participants provided informed consent.

Randomization

Eligible individuals were randomized 1 : 1 to either liraglutide (1.2 mg/day) or a sulphonylurea in addition to metformin. Randomization was revealed after the baseline measurements were recorded. The randomization sequence was computer-generated with a block size of four by an independent statistician and stratified by site (Leicester/Birmingham), pre-study medication (dual/mono), age ($\leq$55 or $>$55 years) and gender. Those individuals on a pre-study regime of metformin plus pioglitazone if randomized to remain on pre-study therapy had pioglitazone switched to a sulphonylurea. Those randomized to liraglutide who were previously taking a sulphonylurea had this discontinued at baseline.

Outcomes

The primary outcome was a composite endpoint of HbA1c $< 7.0\%$, no weight gain (defined as either weight loss or $<$1 kg weight increase) and no severe hypoglycaemic events (requiring hospitalization [17]) assessed 12 weeks post Ramadan.

The main secondary outcome was a composite endpoint of HbA1c $< 7.0\%$, weight reduction (weight loss $\geq$1 kg) and no severe hypoglycaemic events 12 weeks post Ramadan.

Further secondary outcomes included change in HbA1c, weight, BP, lipid profile, severe hypoglycaemia and also a composite endpoint of reduction in weight (weight loss $\geq$1 kg) and improved HbA1c (reduction $\geq$0.3%), a composite endpoint of reduction in weight and no severe hypoglycaemic events, a composite endpoint of improved HbA1c and no severe hypoglycaemic events, and change in treatment satisfaction and physical activity. All outcomes were recorded at both 3 and 12 weeks post Ramadan. All blood glucose events of $\leq$3.9 mmol/l recorded in glucose monitoring diaries over the entire study period were collected and reported as a secondary outcome.

Sample Size

The sample size required to detect a difference of 22% in those achieving the primary composite outcome between those receiving liraglutide and those receiving a sulphonylurea was 120 participants (n = 60 per group), with 80% power and an alpha of 5%, assuming a dropout rate of 15%. This was calculated from the Liraglutide Effect and Action in Diabetes (LEAD) trials which reported that 32% of people on 1.2 mg daily of liraglutide met the composite endpoint (HbA1c $< 7.0\%$, no weight gain and no hypoglycaemia) compared with 8% in the glimepiride arm [23].

Procedures

Liraglutide was started at 0.6 mg/day administered subcutaneously in the evening and titrated to 1.2 mg/day for the duration of the study following a 14-day run-in period. Those already receiving a sulphonylurea remained on their previous sulphonylurea (included gliclizide, glimepiride and one patient on glibenclamide) with advice to administer the dose once daily in the evening, if on a twice daily dose investigators were advised to recommend best practice which was to administer half the previous morning dose in the morning and half in the evening. Those switching from pioglitazone or commencing a sulphonylurea, the choice of the sulphonylurea was left to the investigator but included either gliclizide or glimepiride and the dose was advised to be administered in the evening and titrated up over 2–4 weeks. The three sulphonylureas used in the trial included gliclizide (n = 44), glimepiride (n = 4) and glibenclamide (n = 1). The mean dose and dose range used is shown in Table S1, Supporting information. Background treatment with metformin remained stable throughout the study. Participants who did not tolerate trial treatment continued to be followed up. At baseline, 3 and 12 weeks post end of Ramadan the following data were collected: weight, body mass index (BMI), BP, waist and hip circumference, HbA1c, total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, triglycerides and all current medication. Standard operating procedures were used to ensure consistent data collection across both sites [24].

A number of methods were employed to capture data pertaining to frequency and severity of previous (either before Ramadan) or current (between study visits) hypoglycaemia. These include a hypoglycaemia questionnaire that was completed by the study clinician which included questions around the frequency of hypoglycaemic episodes with differing severity. At the end of the study data on hospital admissions in the previous 12 months and over the month of Ramadan that were associated with diabetes were collected from medical records.

Self-reported hypoglycaemia was captured as participants were instructed to record their blood glucose levels approximately five times a day throughout the duration of the study and to record any self-reported hypoglycaemic events in a specially designed blood glucose monitoring diary provided to them. Each participant received information about the finger stick testing and hypoglycaemia from the study nurse. All participants were provided with testing strips and glucose monitors where necessary.

Treatment satisfaction was assessed via the self-administered Diabetes Treatment Satisfaction Questionnaire (DTSQ) [25]. There are two separate items to measure perceived frequency of hyperglycaemia and perceived frequency of hypoglycaemia using a scale ranging from 0 (none of the time) to 6 (most of the time). Physical activity was assessed using the self-administered International Physical Activity Questionnaire (IPAQ) [26].

Safety and tolerability were assessed by reviewing reported adverse events during the study. All adverse events were rated by the study site investigators for intensity and relationship to study drug.

Statistical Analyses

All analysis was carried out on a complete case basis according to randomized group. As a sensitivity analysis, for the primary and main secondary outcome multiple imputation was used to perform an intention to treat analysis and a per protocol analysis excluding those who were no longer taking their randomized treatment at the two follow-ups was also performed. All analyses were performed at both time points.

Weight reduction is defined as a weight loss $\geq$1 kg. No weight gain is defined as either weight loss or $<$1 kg weight increase. Improved HbA1c is defined as a reduction of $\geq$0.3%. Deterioration of HbA1c is defined as increase of $\geq$0.3%.

The primary outcome was analysed using logistic regression adjusted for the stratification factors (site, prior therapy, age and sex) the dependent variable was defined as those achieving all of the composite end point targets. The same analysis method was used for the secondary composite outcomes. The biomedical outcomes were analysed using linear regression adjusted for the stratification factors and baseline value (due to an imbalance in baseline characteristics). Ordinal regression was used to compare treatment groups for the treatment satisfaction scores, linear regression was used for total metabolic equivalent tasks (METs).

The percentage of patients experiencing at one or more self-reported hypoglycaemic events in their diaries (defined as a blood glucose reading $\leq$3.9 mmol/l) was reported by group along with the median [interquartile range (IQR)] number of episodes per patient. The incidence rate of hypoglycaemia per person year was calculated per group and compared using the incidence rate ratio (IRR).

All analyses were carried out in STATA (version 12.0), 95% confidence intervals (CIs) are shown throughout and $p < 0.05$ relates to statistical significance.

Results

Table 1 show the baseline characteristics by group, 52 participants were randomized to the metformin plus sulphonylurea group, with 47 to the metformin plus liraglutide group. The groups were evenly matched in terms of the prior therapy (mono and dual). Low levels of missing data were seen across all characteristics apart from HDL and LDL cholesterol. The mean age of participants was 51.8 years (s.d. 10.8), with 50% being male. The groups were well balanced in terms of biomedical, medical history, medication and family history. Higher levels of baseline weight, waist, hip and BMI were seen in the liraglutide group.

Primary and Main Secondary Outcome

Follow-up data was available for 78 participants at 3 weeks post Ramadan and 67 participants 12 weeks post Ramadan (Figure 1). Four participants in the Metformin plus sulphonylurea group (10.3%) met the primary composite outcome compared with eight (26.7%) in the liraglutide group 12 weeks post Ramadan, complete case analysis odds ratio (OR) 4.08, 95% CI 0.97, 17.22. The intention to treat analysis showed a slightly more conservative result, OR 3.51, 95% CI

Table 1. Baseline characteristics.

	Metformin + sulphonylurea 52 (52.5)	Metformin + liraglutide 47 (47.5)
Anthropometrical data		
Age, years	52.2 (10.7)	51.5 (11.1)
Sex, male	26 (50.0)	24 (51.1)
Ethnicity		
Indian	34 (66.7)	25 (52.2)
African	0 (0)	2 (4.3)
Bangladeshi	4 (7.8)	5 (10.6)
Pakistani	9 (17.7)	10 (21.3)
Other Asian	4 (7.8)	5 (10.6)
Weight, kg	79.0 (11.2)	86.1 (16.9)
Waist, cm	102.4 (11.3)	105.7 (12.8)
BMI, kg/m^2	30.1 (4.3)	33.0 (7.3)
Smoking*		
Non/Ex	41 (85.4)	37 (86.1)
Current	7 (14.6)	6 (13.9)
Biomedical data		
Cholesterol, mmol/l*	4.3 (0.7)	4.2 (0.8)
Trigs, mmol/l*	2.6 (1.3)	2.2 (1.9)
HDL, mmol/l†	1.0 (0.3)	1.1 (0.3)
LDL, mmol/l†	2.2 (0.8)	2.0 (0.6)
HbA1c, %	7.8 (1.0)	7.6 (1.1)
Systolic BP, mm Hg	132.2 (16.3)	130.8 (16.1)
Diastolic BP, mm Hg	83.7 (9.0)	84.8 (9.3)
Medication data		
Prior therapy – metformin only	28 (53.9)	25 (53.2)
Prior therapy – dual	24 (46.2)	22 (46.8)
SU/metformin	23 (95.8)	21 (95.5)
Pioglitazone/metformin	1 (4.2)	1 (4.5)
Antihypertensive	23 (45.1)	24 (51.1)
Lipid lowering	32 (62.8)	26 (55.3)
Medical history		
Prior CVD	7 (13.5)	4 (8.5)
Hypertension	22 (43.1)	24 (51.1)
Patient satisfaction		
Total score†	32 (26, 36)	30 (27, 34)
Perceived frequency of hypoglycaemia†	1 (0, 3)	1 (0, 3)
Perceived frequency of hyperglycaemia†	2 (0, 3)	3 (0, 4)
Physical activity		
Total METS†	1604.7 (1997.8)	1371.4 (1630.1)

Data given as n (%) for categorical variables, mean (s.d.) for continuous, median (IQR) for ordinal. CVD: MI, heart valve disease, heart failure, atrial fibrillation, angina, stroke, angioplasty/CABG, leg angioplasty/bypass, peripheral vascular disease. BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass graft; CVD, cardiovascular disease; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; HbA1c, haemoglobin A1c; METS, metabolic equivalent tasks; SU, sulphonylurea.

*Five or more missing items.

†Ten or more missing items.

0.90, 13.62. Similar results were seen at the earlier time point of 3 weeks post Ramadan with more participants in the liraglutide group achieving the composite outcome compared with the sulphonylurea group (38.2 vs. 20.9%, OR 2.99, 95% CI 1.00, 8.97). Across both time points significantly more participants met the composite of HbA1c < 7.0%, weight reduction and no severe hypoglycaemia in the liraglutide group compared with the sulphonylurea group, with an adjusted odds of a good outcome 12-fold higher (OR 12.42, 95% CI 2.66, 58.11) in the liraglutide group compared with the sulphonylurea group at 3 weeks post Ramadan (Table 2).

Biomedical Outcomes

The biomedical outcomes are shown by group in Table 3. From a baseline of 7.7%, there was no change in HbA1c at 12 weeks post Ramadan in the sulphonylurea group (+0.02%) compared with a 0.32% reduction in the liraglutide group (coefficient −0.41, 95% CI −0.83, 0.01). A significant difference in HbA1c was seen between groups at the earlier time point of 3 weeks post Ramadan (coefficient −0.30, 95% CI −0.56, −0.04). At both time points a significant reduction in weight was seen in the liraglutide group compared with the sulphonylurea group, at 12 weeks post Ramadan −2.57 kg compared with +0.25 kg respectively. Lower levels of diastolic BP was also seen in the liraglutide group at 12 weeks post Ramadan.

Patient Satisfaction Questionnaire and Physical Activity

Treatment satisfaction was high at baseline, showed no deterioration during the study and was comparable across the treatment groups; the perceived frequency of hypoglycaemia was significantly higher in the sulphonylurea group at first follow-up compared with the liraglutide group (Table 3). No difference in self-reported physical activity was found either between groups or over time (Table 3).

Hypoglycaemia

There were no severe hypoglycaemic events (requiring hospitalization) in either group. Using a cut point of ≤3.9 mmol/l to define hypoglycaemia from the self-monitoring diaries, 46.2% of participants in the sulphonylurea experienced one or more events during the study compared with 25.0% in the liraglutide group, with a median of three events per participant in the sulphonylurea group compared with two in the liraglutide group (Table 4). The incidence rate of hypoglycaemia was 10.5 per person year in the sulphonylurea group compared with 3.0 per person year in the liraglutide group (IRR 0.29, 95% CI 0.19, 0.41). Excluding two participants with extreme reporting of hypoglycaemia in the sulphonylurea group did not change the overall interpretation (IRR 0.58, 95% CI 0.39, 0.84).

Adverse Events

There were three adverse events reported during the study. Two in the liraglutide group and one in the sulphonylurea group. The participant in the sulphonylurea group reported generally feeling unwell with no specific symptoms, this was not related to the study drug. In the liraglutide arm, one participant reported tingling/numbness in their feet, this was thought to be related to the study drug and the dose of liraglutide was reduced from 1.2 to 0.6 mg/day. The other participant in the liraglutide group had hyperglycaemia which was unrelated to the study drug.

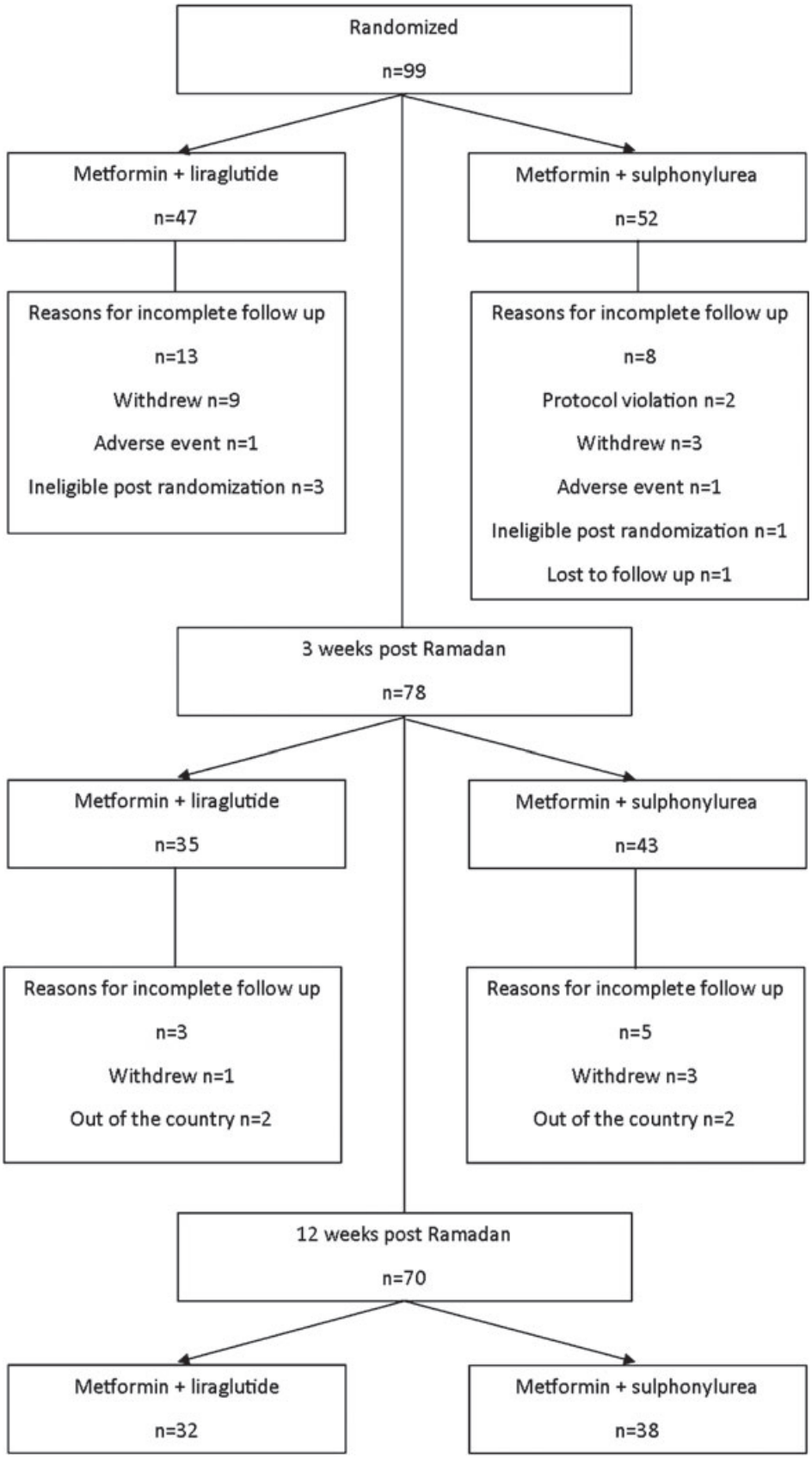

Figure 1. Flow diagram.

Table 2. Primary outcome and main secondary outcome.

Composite	3 weeks post Ramadan					12 weeks post Ramadan				
	n	Metformin + sulphonylurea	Metformin + liraglutide	Adjusted OR (95% CI)	p Value	n	Metformin + sulphonylurea	Metformin + liraglutide	Adjusted OR (95% CI)	p Value
HbA1c < 7.0%, no weight gain, no severe hypo*										
Complete case	77	9 (20.9)	13 (38.2)	2.99 (1.00, 8.97)	0.05	69	4 (10.3)	8 (26.7)	4.08 (0.97, 17.22)	0.06
Intention to treat†	99	—	—	2.62 (0.84, 8.20)	0.10	99	—	—	3.51 (0.90, 13.62)	0.07
Per protocol	68	9 (21.4)	13 (50.0)	4.48 (1.42, 14.14)	0.01	48	2 (6.7)	5 (27.8)	7.45 (1.07, 51.87)	0.04
HbA1c < 7.0%, weight reduction, no severe hypo*										
Complete case	77	3 (7.0)	13 (38.2)	12.42 (2.66, 58.11)	0.001	69	3 (7.7)	8 (26.7)	6.30 (1.25, 31.72)	0.03
Intention to treat†	99	—	—	11.16 (2.43, 51.26)	0.002	99	—	—	4.63 (1.11, 19.40)	0.04
Per protocol	68	3 (7.1)	13 (50.0)	17.55 (3.64, 84.50)	<0.0001	48	2 (6.7)	5 (27.8)	7.45 (1.07, 51.87)	0.04

Data shown n (%) achieving all targets, p value from logistic regression adjusted for group (mono and dual), site, age, sex. CI, confidence interval; OR, odds ratio.

*Severe hypo defined as a hypoglycaemic event requiring hospitalization.

†Missing values imputed using multiple imputation.

Discussion

The results show that liraglutide, as an adjunct to metformin therapy, compared with a sulphonylurea in people with established T2DM observing Ramadan results in a greater proportion achieving the composite end point of HbA1c < 7.0%, no weight gain and no severe hypoglycaemic events, defined as requiring hospitalization. Significantly more people receiving liraglutide therapy also achieved the composite end point of HbA1c < 7% with a reduction in body weight and no severe hypoglycaemic events. A significant reduction in HbA1c levels was observed in those receiving liraglutide at both time points with a between group difference reaching statistical and clinical significance. This infers that glycaemic control in those receiving liraglutide was not only stabilized but improved during Ramadan. Although no severe hypoglycaemic events were observed in either group, significantly more participants in the sulphonylurea group experienced one or more hypoglycaemic events during the study compared with the liraglutide group. This improvement in glycaemic control accompanied by the low incidence of non-severe hypoglycaemic events and non-occurrence of severe hypoglycaemia makes this an extremely helpful treatment strategy in this group. A significant reduction in body weight was also observed in the liraglutide group compared with weight maintenance in the sulphonylurea group. There appeared to be no difference in the outcomes whether patients were on mono or dual therapy prior to randomization (data not shown).

To our knowledge this is the first randomised controlled trial (RCT) comparing a sulphonylurea to a GLP-1 receptor agonist in patients with established T2DM who fast during Ramadan. Five recent studies have investigated the effect of a DPP-4 inhibitor on incident hypoglycaemia in comparison to a sulphonylurea during Ramadan [27–31]. Al Sifri demonstrated, in a large multi-centred open labelled RCT, a significant reduction in the risk of self-reported symptomatic hypoglycaemia in patients receiving sitagliptin (a DPP-4 inhibitor) versus a sulphonylurea (IRR 0.51, 95% CI 0.34, 0.75; p < 0.001) [27]. While this was a large trial the primary outcome was based on symptomatic hypoglycaemia not confirmed by self-monitoring of blood glucose. Furthermore no effects on weight or HbA1c levels were reported. These results are further supported by a similar RCT conducted in Indian and Malaysian patients again reporting an approximate 50% reduction in the risk of self-reported symptomatic hypoglycaemia during Ramadan in those receiving sitagliptin compared with a sulphonylurea [28]. Vildagliptin, another DPP-4 inhibitor, has been associated with significantly lower incidence of hypoglycaemic events compared with sulphonylurea during Ramadan and concomitant reduction in HbA1c in a number of prospective observational studies [29–31]. However, some of these studies have major design flaws which make the data difficult to interpret with hypoglycaemia data collected via self-report rather than by an objective measure [29–31].

Collectively these results with DPP-4 inhibitors offer some support for the use of incretin based therapies as a second line therapeutic option for patients with T2DM participating in Ramadan due to their associated low risk of hypoglycaemia. Moreover, these data add to the growing body of evidence that illustrate an association between increased risk of hypoglycaemia and the use of sulphoylureas during Ramadan [27–30]. Our results additionally indicate liraglutide as a potentially more effective therapeutic option than a sulphonylurea during Ramadan because weight-loss was also observed and no significant difference in treatment satisfaction between the groups. Although this is of importance given liraglutide is injectable which one would expect to be less acceptable to the patient than an oral therapy particularly during Ramadan, this result should be interpreted with some caution as a differential withdrawal rate was seen, with more participants in the liraglutide group withdrawing than the sulphonylurea group (21.3 vs. 11.5%). Treatment satisfaction scores were not collected from those choosing not to take any further part in the study. Reassuringly, when imputing the missing treatment satisfaction scores (data not shown) the interpretation of this data does not change, also participants who did not tolerate the trial treatment were continued to be followed up and data on treatment satisfaction were sought in these cases. Furthermore, the overall treatment satisfaction score is higher than that previously reported for liraglutide

Table 3. Secondary outcomes.

	3 weeks post Ramadan					12 weeks post Ramadan				
Biomedical outcomes	n	Metformin + sulphonylurea Mean (s.d.)	Metformin + Liraglutide Mean (s.d.)	Coefficient (95% CI)	p Value	n	Metformin + sulphonylurea Mean (s.d.)	Metformin + Liraglutide Mean (s.d.)	Coefficient (95% CI)	p Value
HbA1c (%)	77	−0.27 (0.60)	−0.54 (0.87)	−0.30 (−0.56, −0.04)	0.03	69	0.02 (0.81)	−0.32 (1.22)	−0.41 (−0.83, 0.01)	0.05
Weight (kg)	77	−0.42 (1.57)	−2.23 (2.96)	−1.35 (−2.44, −0.26)	0.02	70	0.25 (2.43)	−2.57 (3.83)	−2.49 (−4.01, −0.97)	0.002
Systolic BP (mm Hg)	75	−4.43 (13.79)	−3.72 (15.46)	2.17 (−3.61, 7.95)	0.46	70	−1.53 (15.54)	−5.23 (15.45)	−1.79 (−8.64, 5.06)	0.60
Diastolic BP (mm Hg)	75	−1.84 (9.09)	−1.98 (8.38)	0.49 (−3.05, 4.03)	0.78	70	−0.65 (8.78)	−6.18 (9.54)	−4.55 (−8.57, −0.53)	0.03
Cholesterol (mmol/l)	72	0.06 (0.51)	0.09 (0.76)	−0.05 (−0.34, 0.24)	0.74	65	−0.13 (0.61)	−0.003 (0.80)	0.03 (−0.27, 0.33)	0.86
Triglycerides (mmol/l)	72	−0.19 (1.04)	0.02 (1.66)	−0.09 (−0.53, 0.36)	0.71	65	−0.56 (1.28)	−0.38 (1.53)	−0.14 (−0.53, 0.25)	0.47
Composite outcomes	**n**	**n (%)**	**n (%)**	**OR (95% CI)**	**p Value**	**n**	**n (%)**	**n (%)**	**OR (95% CI)**	**p Value**
Weight reduction and improved HbA1c	77	9 (20.9)	19 (55.9)	4.62 (1.68, 12.76)	0.003	69	6 (15.4)	11 (36.7)	3.76 (1.08, 13.02)	0.04
Weight reduction and no severe hypo*	77	17 (39.5)	23 (67.7)	3.32 (1.23, 8.95)	0.02	70	12 (30.8)	21 (67.7)	5.75 (1.88, 17.54)	0.002
Improved HbA1c and no severe hypo*	77	22 (51.2)	24 (70.6)	2.47 (0.92, 6.64)	0.07	69	14 (35.9)	15 (50.0)	1.67 (0.59, 4.71)	0.33
Patient satisfaction	**n**	**Median (IQR)**	**Median (IQR)**	**p Value**		**n**	**Median (IQR)**	**Median (IQR)**	**p Value**	
Total score	72	32 (30, 36)	33 (30, 35)	0.77		62	33 (28, 35)	31 (27, 35)	0.79	
Perceived frequency of hypoglycaemia	72	1 (0, 3)	0 (0, 2)	0.05		66	1 (0, 3)	1 (0, 2)	0.40	
Perceived frequency of hyperglycaemia	72	2 (1, 3)	1 (0, 3)	0.39		66	3 (0, 4)	2 (1, 4)	0.97	
Physical activity	**n**	**Mean (s.d.)**	**Mean (s.d.)**	**p Value**		**n**	**Mean (s.d.)**	**Mean (s.d.)**	**p Value**	
Total METS	54	1968.2 (1802.9)	1674.6 (2064.1)	0.58		48	2870.3 (3936.8)	1809.9 (1902.6)	0.26	

For the continuous measures the data is shown as mean change (s.d.), coefficient is the between group difference at follow-up adjusted for the stratification factors and baseline value. For the composite binary measures the data is shown as n (%) achieving all targets, p value from logistic regression adjusted for group (mono and dual), site, age and sex. Patient satisfaction and physical activity – data given as median (IQR), p value from ordinal regression for patient satisfaction and mean (s.d.), p value from linear regression for physical activity. BP, blood pressure; CI, confidence interval; HbA1c, haemoglobin A1c; IQR, interquartile range; OR, odds ratio.

*Severe hypo defined as requiring hospitalization.

doi:10.1111/dom.12249

Table 4. Hypoglycaemia data.

	Metformin + sulphonylurea n = 52	Metformin + liraglutide n = 48	IRR (95% CI)	p Value
Baseline self-reported				
Experienced a hypo in last year, n (%)	15 (30.0)	15 (32.6)		
Number per month, median (IQR)	1.5 (0.2, 2.5)	2.0 (1.0, 4.0)		
Experienced a hypo in last year requiring assistance, n (%)	2 (3.9)	0 (0)		
Experienced a hypo in last year requiring hospitalization, n (%)	0 (0)	0 (0)		
3 weeks post Ramadan				
Experienced a hypo since last visit, n (%)	13 (31.0)	8 (22.9)		0.43
Number since last visit requiring action, median (IQR)	1.5 (1.0, 4.0)	1.0 (1.0, 2.0)		0.44
Experienced a hypo since last visit requiring assistance, n (%)	0 (0)	0 (0)		
Experienced a hypo since last visit requiring hospitalization, n (%)	0 (0)	0 (0)		
12 weeks post Ramadan				
Experienced a hypo since last visit, n (%)	11 (28.2)	5 (16.1)		0.23
Number since last visit requiring action, median (IQR)	4.0 (3.0, 6.0)	1.0 (1.0, 2.0)		0.01
Experienced a hypo since last visit requiring assistance, n (%)	1 (2.6)	0 (0)		0.36
Experienced a hypo since last visit requiring hospitalization, n (%)	0 (0)	0 (0)		
Blood glucose self-monitoring diaries				
Experiencing one or more blood glucose readings ≤3.9 mmol/l, n (%)	24 (46.2)	12 (25.0)		
During Ramadan only	13 (25.0)	6 (12.5)		
Number of episodes ≤3.9 mmol/l, median (IQR)	3 (1, 6)	2 (1, 5)		
Incidence rate per person year	10.5	3.0	0.29 (0.19, 0.41)	<0.0001
Incidence rate per person year*	5.2	3.0	0.58 (0.39, 0.84)	0.003

Data shown as count (%) for binary variables, with between group differences assessed using chi-squared test, median (IQR) displayed for the number of hypos experiences, between group differences assessed using the Wilcoxon test. Incidence rate shown per person year. CI, confidence interval; IQR, interquartile range; IRR, incidence rate ratio.

*Excluding two participants with extreme levels of hypoglycaemia reporting.

in the LEAD-6 trial [mean 15.18 (±0.58)] [17]. This is of relevance given treatment satisfaction is associated with increased adherence and improved clinical outcomes [32]. Our results are supported by Pratley et al who also reported no difference between perceived convenience of treatment between oral sitagliptin and injectable liraglutide [21]. We additionally found, and of relevance in the context of fasting during Ramadan, a significantly lower fear for hypoglycaemia in the liraglutide group which could impact on treatment adherence specifically during prolonged periods of fasting.

The limitation of this is study was not reaching the desired sample size of 120 participants. It is widely accepted that people of South Asian ethnicity residing in the UK are a difficult group to engage in research [33], particularly when requesting participation during a significant religious period such as Ramadan and when the intervention arm included an injectable therapy. However, although underpowered, we were able to demonstrate a 16.4% difference in our primary outcome between those receiving liraglutide and those receiving sulphonylurea, with this comparison reaching statistical significance in the per protocol sensitivity analysis. A further limitation is that this was an open label trial; a double-blind, double dummy RCT would be preferable, however, funding did not permit this type of study design. Another limitation is that we did not compare a GLP-1 receptor agonist with a DPP-4 inhibitor. However, previous studies directly comparing a GLP-1 receptor agonist with a DPP-4 inhibitor when added to Metformin have consistently shown greater efficacy, more weight loss and equivalent or improved treatment satisfaction with the GLP-1 receptor agonist [21,34,35].

The major strengths of this study are that this was a RCT and that hypoglycaemia was objectively measured in addition to other biomedical outcomes. Standard operational procedures were followed by the clinical measurement teams who were fully trained and competent at collecting this type of data. Further, all blood samples were analysed in accredited National Health Service (NHS) pathology laboratories. Blood glucose diaries and equipment were provided to participants so that the incidence of hypoglycaemia could be objectively measured

which is a more robust method of recording this data compared with self-reported or patient recall.

These results indicate that the GLP-1 therapy liraglutide (1.2 mg/day) is an acceptable, well tolerated and safe therapy associated with low risk of hypoglycaemia for use during Ramadan in combination with metformin compared with sulphonylurea, although this trial was underpowered to show a difference on the primary composite outcome, favourable patient outcomes were achieved for HbA1c and weight in addition to a high level of patient treatment satisfaction.

Acknowledgements

The project was funded by an unrestricted investigator initiated grant from Novo Nordisk. The project was supported by the University of Leicester Clinical Trials Unit, M. J. D. is the Director of the CTU, K. K. Deputy Director and L. J. G. is the Senior Statistician. This project was also supported by The National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care – Leicestershire, Northamptonshire and Rutland (NIHR CLAHRC – LNR), and The NIHR Leicester-Loughborough Diet, Lifestyle and Physical Activity Biomedical Research Unit which is a partnership between University Hospitals of Leicester NHS Trust, Loughborough University and the University of Leicester. The guarantor of the manuscript is Prof. Melanie Davies.

The study results were presented the American Diabetes Association Conference (published abstract), European Association for the Study of Diabetes (published abstract, poster presentation) and International Diabetes Federation Diabetes (published abstract, poster discussion).

Conflict of Interest

M. J. D. has received funds for research, honorariums for speaking at meetings, and has served on advisory boards for Lilly, Sanofi Aventis, MSD, Novo Nordisk, BMS, BI and Roche. K. K. has received funds for research, honorariums for speaking at meetings, or served on advisory boards for Astra Zeneca, GSK, Lilly, Novartis, Pfizer, Servier, Sanofi Aventis, MSD and Novo Nordisk. MAS has received honorariums for presenting at meetings from MSD, Novo Nordisk and Sanofi Aventis. Leicester Diabetes Centre, University Hospitals of Leicester and Diabetes & Endocrinology, University Hospital Birmingham participated in the study.

M. J. D., K. K., M. A. S., H. W. conceptualized the project. M. J. D., E. B., L. J. G. drafted the manuscript. L. J. G. analysed the data. M. A. S., H. W., D. S., K. K. commented on the manuscript. All authors approved the final version of the manuscript. M. J. D. is guarantor.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Sulphonylurea medication.

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