Safety and effectiveness of non-insulin glucose-lowering agents in the treatment of people with type 2 diabetes who observe Ramadan: a systematic review and meta-analysis

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Aim: To determine which non-insulin glucose-lowering treatment regimens are most appropriate in people with type 2 diabetes who choose to fast during Ramadan.

Methods: Electronic databases were searched for randomized controlled trials (RCTs) and observational studies that compared non-insulin glucose-lowering agents in people with type 2 diabetes fasting during Ramadan. Those studies which reported hypoglycaemia, weight and glycated haemoglobin (HbA1c) change were included. Data were pooled using random effects models.

Results: A total of 16 studies were included: 9 RCTs and 7 observational studies. There was evidence that dipeptidyl peptidase-4 (DPP-4) inhibitors led to fewer hypoglycaemic events compared with sulphonylureas. Sitagliptin significantly reduced the number of patients with ≥1 hypoglycaemic episodes during Ramadan [risk ratio (RR) 0.48, 95% confidence interval (CI) 0.36, 0.64; p > 0.0001]. This was not replicated in the RCTs of vildagliptin, but a significant reduction was found in the observational studies (RR 0.28, 95% CI 0.10, 0.75; p = 0.01) with high heterogeneity (I² = 86.7%). Significant reductions in HbA1c and weight were seen in the observational studies of vildagliptin versus sulphonylureas. The use of liraglutide led to significant weight loss (−1.81 kg, 95% CI −2.91, −0.71; p = 0.001) compared with sulphonylureas. Pioglitazone significantly increased weight compared with placebo (3.48 kg, 95% CI 2.82, 4.14; p < 0.0001).

Conclusions: The analysis supports the use of DPP-4 inhibitors during Ramadan rather than sulphonylureas for reduction in hypoglycaemia without a cost to diabetes control and weight. The glucagon-like peptide (GLP)-1 agonist liraglutide provides clinical benefits, but more studies are required. RCTs of DPP-4 inhibitors compared with GLP-1 agonists and novel therapies including the sodium-glucose co-transporter 2 and α-glucosidase inhibitors are needed to inform evidence-based guidelines.

Keywords: DPP-IV inhibitor, GLP-1 analogue, meta-analysis, sulphonylureas, systematic review, type 2 diabetes

Introduction

There are over 1.6 billion Muslims worldwide, constituting 23% of the total global population [1]. Ramadan is one of the five pillars of the Islamic faith and represents a significant cultural, religious and social identifier for many Muslims [2]. The majority of Muslims participate in this holy month. Observance of Ramadan requires fasting from dawn to sunset. Abstaining from eating and drinking during daylight hours, most Muslims will consume two meals each day [2]. The timing of Ramadan follows the lunar calendar, therefore, the length of the fast varies depending on the time of year and the geographical location [2], but is usually between 10 and 20 h.

The Quran exempts ‘sick’ people from fasting, including pregnant, lactating or menstruating women, elderly people and those with a chronic illness [2]. Concern for Muslims with diabetes during Ramadan has been recognized by religious leaders and an agreement was signed between the two leading bodies, the Islamic Organisation for Medical Sciences and the International Islamic Fiqh Academy [3] with the aim of helping individuals to make informed decisions about fasting during Ramadan with support from their physicians [4]. Many Muslims with diabetes, however, do not consider themselves to be sick and are eager to fast. The EPIDIAR study [2] identified that 43% of people with type 1 diabetes and 79% of people with type 2 diabetes (T2DM) fasted for at least 15 days during Ramadan. Globally, it is estimated that 50 million Muslims with T2DM fast during Ramadan [5]; however, the proportion of those with T2DM who observe Ramadan varies considerably, with a rate of 58–90% amongst different Islamic countries [2].

The associated risks of fasting by people with diabetes include hypoglycaemia, hyperglycaemia, diabetic ketoacidosis, venous thromboembolisms and dehydration. The EPIDIAR study highlighted an increased risk of severe hypoglycaemia in people with T2DM fasting during Ramadan compared with...
other months of the year [2]. This can lead to discontinuation of medication and/or over-compensating when fast is broken, leading to hyperglycaemia [6]. A number of clinical guidelines for people with diabetes who choose to fast have been published [6–10], but these recommendations are largely based on expert consensus and many health professionals feel poorly qualified to provide some of the recommendations. It is paramount that health professionals respect their patient’s choice to fast whilst simultaneously using their knowledge, based on best evidence, to provide them with the safest management and treatment options.

The aim of the present systematic review and meta-analysis was to evaluate the evidence regarding the safety and efficacy of non-Insulin glucose-lowering regimes in those with T2DM observing Ramadan.

Materials and Methods

A protocol was written before the start of the systematic review and submitted to the PROSPERO repository (http://www.crd.york.ac.uk/PROSPERO/).

Data Sources and Searches

Eligible studies were identified through searches of Medline, Embase and 'OpenGrey' online from 1946 to 8 April 2014. Additional studies were identified with the help of selected academics who have expertise in this area of research.

Study Selection

Eligible study designs included randomized controlled trials (RCTs), non-randomized clinical trials and observational studies including cohort, case–control and cross-sectional studies. Conference abstracts, meta-analysis, systematic reviews, editorials, expert opinions and case reports were excluded.

Patient groups included were adults with T2DM with an intention to fast during Ramadan, who were on a glucose-lowering treatment other than insulin or diet and lifestyle only. Eligible glucose-lowering therapies included: metformin; meglitinides; sulphonylureas; thiazolidinediones; glucagon-like peptide (GLP)-1 receptor analogues; α-glucosidase inhibitors; dipeptidyl peptidase-4 (DPP-4) inhibitors; and sodium-glucose co-transporter 2 (SGLT2) inhibitors. Patient groups excluded were those with type 1 diabetes, those not intending to fast, those with pre-diabetes or impaired glucose tolerance and those not taking any of the glucose-lowering therapies in question.

The primary outcome examined was number of participants having ≥1 hypoglycaemic episode during Ramadan. Secondary outcomes were severe episodes of hypoglycaemia, total number of hypoglycaemic episodes, and weight and HbA1c change 1 month after the end of Ramadan, representing an ~8-week follow-up. This time point was chosen because it was the most often reported follow-up time in the existing literature. A hypoglycaemic episode was defined as patient-reported symptoms of hypoglycaemia or measured blood glucose of <3.9 mmol/l, without symptoms. A severe hypoglycaemic episode was defined as an episode requiring third party assistance. When multiple time points were reported the time point closest to 1 month after Ramadan was analysed for HbA1c and weight.

Data Extraction and Quality Assessment

Two authors independently reviewed papers to assess whether they met the inclusion criteria. The data from the included studies were extracted by two authors, in a standardized format, with any discrepancies resolved by another author.

We assessed the risk of bias of each study. For the RCTs we used the Cochrane Collaboration assessment [11]. Whilst there is no validated tool to assess risk of bias in observational studies, criteria have been published [12]. We used relevant questions from this published checklist to evaluate consistency of inclusion criteria, recruitment strategy and follow-up, high or differential loss to follow-up, assessment of confounding, selective reporting and any other issues that may cause bias. Each area assessed for both types of study was graded as low risk, high risk or unclear.

Data Synthesis and Analysis

Each treatment comparison was analysed separately and analysis was performed by study type (observational and RCTs).

The risk ratio (RR) and 95% confidence intervals (CIs) were used to summarize the effect size for dichotomous outcomes (number of participants with ≥1 hypoglycaemic event, as previously defined, and number of participants with ≥1 severe hypoglycaemic event), and the rate ratio and 95% CIs were calculated for event rates (number of hypoglycaemic episodes per person-year), these were also combined using a random-effects model. Studies reporting no events in both arms were excluded, a 0.5-correction was applied to those reporting no events in a single arm [11]. For the analysis of rates, Ramadan was assumed to be 30 days in duration across all studies, regardless of actual days fasted by participants. The I² statistic was used to quantify the proportion of total variation that was attributable to statistical heterogeneity.

For the continuous outcomes (HbA1c and weight) mean change from baseline and standard deviation for each intervention group was extracted and the weighted mean differences in change from baseline from each study were synthesized using a random-effects model. All studies collected baseline data ranging between 1 and 12 weeks before the start of Ramadan. The majority of the studies included did not report the standard deviation for the change from baseline, therefore, these were imputed using the baseline and follow-up standard deviations and a correlation coefficient, which was derived using individual participant data for the Treat 4 Ramadan study [11,13]. Where standard deviations were not reported at follow-up, these were assumed to be equal to those reported at baseline [11]. Where the number of participants at follow-up was not reported and could not be calculated, this was assumed to be equal to the number randomized [11].

Meta regression including a variable denoting the study type (observational, RCT) was used to assess the difference in pooled treatment effect between study types.

Because of the limited number of studies included, publication bias was not assessed. Stata (version 13) was used for all
Results

Search

The search identified 496 results (Figure 1). Two additional papers were identified as suitable for inclusion by experts in the field [14,15]. Full texts were then sought for 206 papers. Of these, 10 additional duplicates were identified and three papers could not be obtained [16–18]. A total of 16 papers were identified as fulfilling the inclusion criteria. All of the included papers were published in the English language.

Study Characteristics

The study characteristics are shown in Table 1 [13–15,19–31]. The included studies comprised nine RCTs (2927 participants) and seven observational studies (1775 participants). All 16 studies reported hypoglycaemic events: 14 reported the number of participants with $\geq 1$ hypoglycaemic event, 8 reported number of participants with $\geq 1$ severe hypoglycaemic event and 8 reported the total number of hypoglycaemic events. Eleven studies reported change in HbA1c and nine studies reported weight change, for these outcomes the length of follow-up was between 10 and 98 days after Ramadan (a median of 30 and 28 days for HbA1c and weight, respectively). The majority of the studies, of which only two were RCTs, compared vildagliptin with sulphonylureas (n = 7). Two RCTs compared sitagliptin with sulphonylureas, and one RCT compared liraglutide with sulphonylureas. All these studies included background metformin treatment in both arms. One RCT compared sitagliptin and metformin with sulphonylureas alone, four studies (two observational, two RCTs) compared repaglinide with sulphonylureas and one RCT compared pioglitazone with placebo. Of the RCTs, six reported the time when treatment commenced before Ramadan and this varied from 2 weeks up to 3 months.

Risk of Bias Assessments

The results of the bias assessment for RCTs is shown in Figure 2A. Overall there was poor reporting of the randomization and allocation concealment, with only three of the nine RCTs reporting both of these in sufficient detail. The majority of studies were not blinded and used self-reported hypoglycaemia as the primary outcome, which could lead to bias. Only two RCTs were rated as having a low risk of bias across all of the items [14,15].

The assessment of the observational studies is shown in Figure 2B. All of the observational studies included were prospective, following up groups based on their pre-Ramadan treatment regimen. Only one study adjusted for potential confounding [19].
Table 1. Characteristics of included studies.

| Author and year | Interventions | % metformin | Treatment start* (weeks) | Country | Outcomes | Hypoglycaemia |
|-----------------|---------------|-------------|--------------------------|---------|---------------------------------|
| **Randomized controlled trials** | | | | | | |
| Abid 2013 [20] | Sitagliptin + metformin | Sulphonylurea | Only in sitagliptin group | NR Pakistan | Yes | No | No | No | No | No |
| Al-Sifri 2011 [21] | Sitagliptin† | Sulphonylurea† | 92 | 5 | Egypt, Israel, Jordan, Lebanon, Saudi Arabia, United Arab Emirates | Yes | Yes | Yes | No | No |
| Anwar 2006 [22] | Repaglinide | Sulphonylurea | 0 | 12 | Malaysia | No | No | Yes | No | No |
| Aravind 2012 [23] | Sitagliptin† | Sulphonylurea† | 84 | NR | India, Malaysia | Yes | Yes | No | No | No |
| Brady 2014 [13] | Liraglutide† | Sulphonylurea† | 100 | 2 | UK | Yes | No‡ | No | Yes | Yes |
| Hassanein 2014 [15] | Vildagliptin† | Sulphonylurea† | 100 | 8 | Egypt, Lebanon, Tunisia, Russia, Indonesia, Germany, Jordan, Singapore, UK, Turkey, Spain, Malaysia, United Arab Emirates, Kuwait, Saudi Arabia, Denmark | Yes | No‡ | No | Yes | Yes |
| Mafauzy 2002 [24] | Repaglinide | Sulphonylurea | 0 | 6 | Malaysia, UK, France, Saudi Arabia, Morocco | Yes | No | Yes | Yes | No |
| Malha 2014 [25] | Vildagliptin† | Sulphonylurea† | 100 | NR | Lebanon, USA | Yes | Yes | Yes | No | No |
| Vasan 2006 [14] | Placebo | | | | | | | | |
| **Observational studies** | | | | | | |
| Al-Arouj 2013 [26] | Vildagliptin† | Sulphonylurea† | 89 | — | Bangladesh, Egypt, India, Indonesia, Kuwait, Lebanon, Oman, Pakistan, Saudi Arabia, United Arab Emirates | Yes | Yes | No | Yes | Yes |
| Cesur 2007 [27] | Repaglinide | Sulphonylurea | 0 | — | Turkey | Yes | No | No | Yes | No |
| Devendra 2009 [19] | Vildagliptin† | Sulphonylurea† | 100 | — | UK | Yes | Yes | Yes | Yes | Yes |
| Halimi 2013 [28] | Vildagliptin† | Sulphonylurea† or glibenclamide† | 100 | — | France | Yes | Yes | Yes | Yes | Yes |
| Hassanein 2011 [29] | Vildagliptin† | Sulphonylurea† | 100 | — | UK | Yes | Yes | Yes | Yes | Yes |
| Shete 2013 [30] | Vildagliptin† | Sulphonylurea† | 70 | — | India | Yes | No | No | Yes | Yes |
| Sari 2004 [31] | Repaglinide | Sulphonylurea | 0 | — | Turkey | Yes | No | Yes | Yes | Yes |

HbA1c, glycated haemoglobin; NR, Not Reported.

*Time prior to Ramadan when the treatment was initiated.
†Both arms included background metformin treatment.
‡Zero events reported in both arms and therefore excluded from the analysis.
Hypoglycaemia

In the observational studies, a significantly lower number of participants experienced ≥1 hypoglycaemic episode when receiving vildagliptin compared with sulphonylurea during Ramadan (Table 2, Figure 3), this should be interpreted with caution given the high level of heterogeneity (I² = 86.7%). This difference was non-significant when pooling the two RCTs for the same treatments, although overall no difference between the observational and RCT evidence was seen. No difference was seen between vildagliptin and sulphonylurea for severe events. A significantly lower number of participants experiencing ≥1 hypoglycaemic event was seen in the RCTs comparing sitagliptin with sulphonylureas with background metformin and when compared with sulphonylureas alone. This difference remained significant for the studies with background metformin treatment in both arms for severe events.

There were no significant differences between repaglinide or liraglutide versus sulphonylureas, or pioglitazone versus placebo for any of the hypoglycaemic outcomes, although there were limited data for all of these comparisons.

In terms of the number of hypoglycaemic episodes per person-year, although fewer studies reported this outcome, similar results were found, with significantly reduced rates of hypoglycaemia in the observational studies comparing vildagliptin with sulphonylureas and in the RCT comparing sitagliptin with sulphonylureas.

Glycated Haemoglobin and Weight Change

Table 2 shows the combined analysis in the 11 studies that reported change in HbA1c as an outcome 1 month after Ramadan. There was a significant decrease in HbA1c in the observational studies comparing vildagliptin with sulphonylureas and there was an increase in mean HbA1c in the RCTs with the same interventions, but this did not reach statistical significance. There was high heterogeneity in the observational studies (I² = 75.4%). Although no effect was seen in the observational studies of repaglinide versus sulphonylurea, the RCT did show a significant increase in HbA1c in those taking repaglinide.

Change in weight 1 month after Ramadan was reported in nine studies. There was a significant reduction in weight in the participants treated with vildagliptin compared with those treated with sulphonylureas in the observational studies. The RCT comparing liraglutide with sulphonylureas showed significantly more weight lost in the liraglutide group than in those receiving sulphonylureas. In the RCT comparing pioglitazone with placebo there was significant weight gain in the pioglitazone group.

Discussion

This is the first systematic review assessing non-insulin glucose-lowering therapies in people with T2DM observing Ramadan. Although this review included data from nine completed RCTs, these were spread across a number of comparisons, with a maximum of two RCTs included in any one analysis. These data were complemented by a number of observational studies but, given the potential for bias, less weight should be given to the results from these. Overall, the current evidence base is limited, with many opportunities for future research.

Overall, the results for the hypoglycaemia outcomes were mixed, with the majority of comparisons showing no effect;
### Table 2. Hypoglycaemia during Ramadan and glycated haemoglobin and weight change after Ramadan.

| Study | Participants experiencing ≥1 hypoglycaemia episode during Ramadan | Participants experiencing one or more severe hypoglycaemia episodes during Ramadan | All hypoglycaemic episodes per person-year during Ramadan | HbA1c change post Ramadan | Weight change post Ramadan |
|-------|---------------------------------------------------------------|--------------------------------|--------------------------------------------------|----------------|---------------------|
|       | **No trials** | **RR* (95% CI)** | **p** | **I²** | **Interaction†** | **No trials** | **WMD (95% CI)** | **P** | **I²** | **Interaction†** |
|       | **Vildagliptin vs sulphonylurea‡** | **RCTs** | **Observational studies** | **Vildagliptin vs sulphonylurea‡** | **RCT** | **Observational studies** | **Repaglinide vs sulphonylurea** | **RCTs** | **Observational study** | **Liraglutide vs sulphonylurea‡** | **RCT** |
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however, we did find a significantly lower number of all and severe episodes of hypoglycaemia in participants treated with DPP-4 inhibitors (vildagliptin and sitagliptin) during Ramadan compared with those treated with sulphonylureas. This was not unexpected, given the differing mechanisms of action of these drugs. Sulphonylureas are still the most common second-line therapy for T2DM, in combination with metformin, because of their efficacy, tolerability and low cost [32,33]. The American Diabetes Association recommends that they are used with caution during Ramadan, however, because of their associated increased risk of hypoglycaemia [6]. More recently, the avoidance of long-acting sulphonylureas has been recommended [34]. DPP-4 inhibitors are associated with a lower risk of hypoglycaemia which makes them a suitable treatment choice in patients who chose to fast.

In the present review, we found a significant decrease in HbA1c 1 month after Ramadan with vildagliptin compared with sulphonylureas in the observational studies only, which might suggest that this reduction in the number of hypoglycaemic episodes does not come at a cost to overall glucose control. Furthermore, we found a greater reduction in weight with vildagliptin compared with sulphonylureas. Again, this was an expected outcome as sulphonylureas are typically associated with a weight gain of 1–4 kg [35] and DPP-4 inhibitors are reportedly weight-neutral [36]; however, this is outside of the context of prolonged fasting and, indeed, the reported results provide further evidence of the potential benefits of this therapy during Ramadan beyond improved glycaemic control. Importantly, the two RCTs did not show statistical differences in HbA1c and weight with vildagliptin over sulphonylureas.

It should be noted that none of the studies included in the present systematic review collected data on diet and, where physical activity was measured, it was by self-report. These data are important because of the potential for over-eating at the break of fast and the potential impact of this on glucose control. Future studies should consider collecting data on changes in overall caloric intake, energy expenditure and diet composition.

Three RCTs compared sitagliptin with sulphonylureas. The meta-analysis of the two RCTs using background metformin in both arms showed significantly fewer hypoglycaemic episodes and severe hypoglycaemic episodes when compared with sulphonylureas during Ramadan. No trials have published data regarding change in HbA1c or weight for this comparison. Current National Institute for Health and Care Excellence (NICE) guidelines support the use of DPP-4 inhibitors if there is a risk of hypoglycaemia or if sulphonylureas are contraindicated or not tolerated [37]. In the present review, we suggest that DPP-4 inhibitors may be at least as effective as sulphonylureas in terms of improved glycaemic control during prolonged fasting, in addition to providing a reduced risk of hypoglycaemic events.

The studies comparing repaglinide with sulphonylureas were generally older (2002–2007) than those assessing DPP-4 and GLP-1 agonists (2009–2014). Repaglinide no longer forms part of the first-line treatment for T2DM, therefore, these results have been reported only for the completeness of the present review. Where pioglitazone was compared with placebo there was a significant increase in weight in the pioglitazone group, but the study authors attribute this mean 3-kg weight gain to oedema [14].

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**Figure 3.** Forest plot showing the risk of experiencing ≥1 hypoglycaemic event in those taking dipeptidyl peptidase-4 (DDP-4) inhibitors versus those taking sulphonylureas (SU) with background metformin treatment. RR, risk ratio; RCT, randomized controlled trial.
The Treat 4 Ramadan study was the first RCT to compare a GLP-1 receptor agonist, liraglutide, with sulphonylureas [13]. That study was positive with regard to its primary outcome, a composite of HbA1c <7.0%, no weight gain and no severe hypoglycaemia, and showed a significant weight reduction of −1.8 kg in this analysis. When assessing the number of participants experiencing ≥1 hypoglycaemic event during Ramadan, no difference was found between liraglutide and sulphonylureas. By contrast, when assessing the levels of hypoglycaemia over the duration of the trial, the study reported a significantly lower incidence rate per person-year in the liraglutide arm (incidence rate ratio 0.58, 95% CI 0.39, 0.84; p = 0.003) [13]. A significant HbA1c reduction was also seen in the liraglutide arm when adjusting for the stratification factors and baseline value [13]. Collectively these results support the potential use of a GLP-1 receptor agonist during Ramadan.

Implications for Practice

With a projected 55% increase in the total number of people with diabetes globally by 2035, the future burden of T2DM is set to increase [38]. The prevalence is projected to nearly double in the Middle East and North Africa and to increase by 70% in South-East Asia [38]. Three of the top 10 countries for the prevalence of T2DM are in the Middle East (Kuwait 23%, Saudi Arabia 24% and Qatar 23%) [38]. With high numbers of Muslim patients with T2DM fasting in Ramadan in the Middle East, evidence-based clinical guidelines are needed. Whilst the present review highlights areas where further research is needed, it also provides guidance for clinicians based on the evidence available; we found that DPP-4 inhibitors were superior to sulphonylureas during Ramadan with respect to hypoglycaemia and weight and that GLP-1 receptor agonists also show clinical advantages as assessed by a composite endpoint [13]. As such, clinicians should consider switching patients with T2DM not receiving insulin therapy and who choose to fast during Ramadan from sulphonylureas to these therapies. We would recommend doing this before Ramadan so that a stable dose can be established before Ramadan begins. Clinicians should also counsel patients using evidence-informed guidelines, with the overall benefit of reducing the risk of adverse events during Ramadan. The STEADEXST study highlights the benefits of combining DPP-4 inhibitors with non-drug interventions [15]. The study incorporated individualized Ramadan-focused advice, with more contact between the patient and clinician than might otherwise occur [15]. Indeed, focused education has been shown to decrease the number of hypoglycaemic events in patients with T2DM on non-insulin treatment [39].

Implications for Research

The present analysis highlights the need for more robust blinded large prospective RCTs looking at non-insulin glucose-lowering agents during Ramadan. These studies need to be carried out in different geographical regions with different Muslim populations and preferably to have subjects enrolled across a 12-month period that includes Ramadan. The latter would allow us to determine if the benefit of such medications is greater than that observed in patients outside the context of Ramadan.

No studies have compared GLP-1 agonists with DPP-4 inhibitors head to head during Ramadan. and nor have there been trials examining other non-insulin glucose-lowering agents, such as SGLT2 inhibitors and α-glucosidase inhibitors. Three SGLT-2 inhibitors have been approved for use in the European Union, with more in development worldwide [40]. Dapagliflozin reduces fasting glucose with no more hypoglycaemia than placebo [40]. Similarly, empagliflozin has been reported to improve glycaemic control; again, without an increased the risk of hypoglycaemia [42]. Given the likely increase in use and seemingly favourable side effect profiles, studies to examine these drugs in patients fasting for Ramadan would be beneficial. Some clinicians may be apprehensive to recommend this class of drugs, however, as SGLT2 inhibitors increase glucose urea and thus are associated with increased urination, which may increase the risk of dehydration, particularly in the context of prolonged fasting. This raises a pertinent clinical question that requires answering. Acarbose, an α-glucosidase inhibitor forms part of the NICE guidelines for T2DM but no studies have compared its use during Ramadan with other glucose-lowering agents [37]. The single trial involving thiazolidinediones (pioglitazone) only used placebo as a comparison. Trials to compare thiazolidinediones against other agents would be beneficial.

Strengths and Limitations

There are a number of limitations to the data available for the present systematic review. In certain publications, not all of the necessary statistical information was available on confidence intervals and standard deviations. Where this was the case, information gained from similar studies was used in order that the study could be included in the analysis. In addition, seven of the studies included were observational studies. Potential effects of external confounders that have not been adjusted for on the results of the present review cannot be excluded. In the observational studies comparing DPP-4 inhibitors with sulphonylureas, confounding is likely to have been a particular issue. DPP-4 inhibitors represent a newer drug class compared with sulphonylureas [37]. Patients on DPP-4 inhibitors may have been started on that medication because of worse glycaemic control or issues with weight gain or hypoglycaemia and this may have biased the interpretation of the studies.

Unfortunately, it was not possible to obtain full text for three publications identified in the initial literature search, although we think this is unlikely to have affected the results. One paper written in German did not refer to a drug intervention in the title [16] and the titles of the other two papers [17,18] both suggested that they were not interventional studies.

Of the RCTs, only two trials involved any sort of blinding [14,15]. Patients and clinicians were aware of the treatment given in seven of the RCTs and this may have affected the results. As all studies reported hypoglycaemic episodes based partly or fully on self-reported patient symptoms, the effect of bias in the way in which patients reported symptoms cannot be excluded. Future studies may wish to consider using continuous
glucose monitoring during Ramadan for an objective measure of hypoglycaemia.

Given these limitations in the data collected, the overall strength of the present review is that it was possible to analyse all of the available published data as appropriate. Data from nearly 5000 participants in 24 different countries were analysed to provide the basis of this meta-analysis.

Conclusion

Overall, the present systematic review and meta-analysis summarizes the existing small evidence base. It suggests that DPP-4 inhibitors, and possibly GLP-1 receptor agonists, could be used during Ramadan rather than sulphonylureas for fewer hypoglycaemic episodes and a greater reduction in weight and possibly HbA1c concentration. The results should be interpreted with caution, however, given the variable quality of the studies included. Clinicians can use this review to provide guidance based on the evidence available on how to manage drug therapy in T2D diabetes during Ramadan in those patients not taking insulin. There remains considerable need for further high-quality research, specifically in light of emerging new therapies.

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Conflict of Interest

M. J. D. has received funds for research, honoraria 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, honoraria for speaking at meetings, or served on advisory boards for Astra Zeneca, GSK, Lilly, Novartis, Pfizer, Servier, Sanofi Aventis, MSD and Novo Nordisk.

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