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REVIEW

Filling the Knowledge Gap in Diabetes Management During Ramadan: the Evolving Role of Trial Evidence

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ABSTRACT

Muslim patients with type 2 diabetes (T2D) who fast during Ramadan face challenges in diabetes management due to substantial alterations in lifestyle and treatment that frequently accompany the decision to fast. International guidelines for treating T2D do not fully address the clinical issues unique to fasting, and other guidance documents lack the large and high-quality evidence base available for non-fasting conditions. We reviewed 10 randomized controlled trials and 20 observational studies in T2D during Ramadan to assess the quality of evidence and identify issues in trial design that should be addressed in future studies. Results indicated that heterogeneity in key aspects of trial design precluded meaningful comparisons across studies. These included patients' baseline treatment at entry; use of a cutoff for glycemic control [glycated hemoglobin (HbA_{1c})] for eligibility; exclusion of patients with a history of recurrent hypoglycemia or hypoglycemia unawareness, or with other serious systemic diseases; duration of treatment and follow-up, selection of safety versus efficacy as primary end point; and definition and measurement of those end points. Fructosamine was rarely used as an efficacy end point, despite the advantage of reflecting glycemic control over a period more closely aligned with the duration of Ramadan fasting than HbA_{1c}. Adherence to treatment, definition and adherence to fasting, and changes in diet and exercise were reported inconsistently, and when reported, not in a fashion that would allow adequate control of confounding due to these variables. Despite a large body of evidence demonstrating their safety and efficacy in non-fasting populations, only two trials reported data for glucagon-like peptide-1 analogs, and neither involved a head-to-head comparison against dipeptidyl peptidase-4 inhibitors. More rigorous studies using trial designs suited to the unique conditions of a fasting population and

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capturing both standardized efficacy and safety end points are needed to provide better guidance to optimal treatment of T2D during Ramadan fasting.

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INTRODUCTION

Fasting during the holy month of Ramadan is an important religious obligation for observant Muslims, and it is estimated that about 79% of Muslims with type 2 diabetes (T2D) will fast during Ramadan [1]. Typically, fasting requires refraining from eating, drinking, and use of oral and parenteral medications during the period from 75 min before sunrise to 15 min after sunset [2–4]. Because the occurrence of Ramadan follows the lunar calendar, which is shorter than the Gregorian calendar, the holy month is observed 10–11 days earlier each year. When Ramadan falls during the summer months, the duration of fasting each day could potentially exceed 20 h for people living in northern latitudes where the day is longer [4, 5].

Extended fasting of any sort counteracts some of the main principles of good diabetes management, which traditionally involve careful planning of dietary intake, taking regular meals and exercise, and aligning these activities with any medical treatments used to lower blood glucose, to avoid excessive hyperglycemia and hypoglycemia. Introducing fasting while also using glucose-lowering medications may further challenge diabetes management, particularly with respect to hypoglycemia. Indeed, medical opinion remains divided about whether it is safe, even for people with well-controlled diabetes, to fast during Ramadan [6–9]. These safety concerns are supported by some empirical data. For example, one large survey of 11,173 Muslims with T2D, 78.4% of whom were treated with oral antidiabetic drugs (OADs), indicated that fasting during Ramadan was associated with a 7.5-fold greater incidence of severe hypoglycemia (0.03 ± 0.28 vs. 0.004 ± 0.02 episodes/month, $P < 0.0001$, for fasting vs. non-fasting periods, respectively) [1]. Fasting was also associated with a greater incidence of severe hyperglycemia (0.05 ± 0.35 vs. 0.01 ± 0.05 episodes/month, respectively, $P < 0.0001$). Nevertheless, Ramadan is an integral part of life for many Muslims, with benefits for physical, mental, and social well-being [10], and many Muslims with T2D choose to fast during Ramadan, some against medical advice.

Given that the growing Muslim population of the world often overlaps with regions where the incidence of T2D is also increasing rapidly [11, 12], there is a compelling need for a more rigorous evidence base to help clinicians make informed decisions on how to best treat patients with T2D who wish to fast. For the general population of patients with T2D, several major guideline documents have been published, which include recommendations for newer treatments, such as drugs of the incretin class [glucagon-like peptide-1 (GLP-1) analogs and dipeptidyl peptidase-4 (DPP-4) inhibitors], which have been shown to have a favorable balance of safety and efficacy [13, 14].

Although a variety of other guidance documents have been published offering recommendations on diabetes management during religious fasting [3, 15–25], there is currently no gold standard based on comprehensive, up-to-date, evidence-based recommendations. A major reason is that evidence from clinical trials in non-fasting

populations, which form the basis for major international diabetes treatment guidelines, is not completely transferable to populations who engage in religious fasting. This is because fasting during Ramadan typically results in a variety of changes in lifestyle and treatment, discussed below, which may disrupt typical diabetes management practices.

The most consistent changes occurring during Ramadan fasting include alterations in the typical between-meal interval, reduced frequency of meals (e.g., two per day, instead of three [23, 26]), the type of food eaten (e.g., more fried foods and/or the proportion of energy from carbohydrates such as dates, juices, and sweets vs. other macronutrients) [11], and eating a larger volume of food at a given time if only two meals are consumed. With respect to consistency of exercise, long-night Taraweeh prayers lasting 1–2 h, although not mandatory, can be strenuous [21]. It has also been noted that fasting during Ramadan may be associated with changes in sleep patterns and quality, alertness, and irritability [5]. It is possible, although currently speculative, that the stress of coping with these additional challenges for an entire month could further compromise a person's ability to manage their diabetes effectively.

For patients using OADs, it can be difficult to coordinate taking medications that must or may be administered more than once daily (e.g., some sulfonylurea s or glinides) with an altered meal schedule [27]. Maintaining adequate glycemic control when using OADs may be further complicated if accompanied by arbitrary patient-initiated changes in dose, frequency of dosing, and/or timing of administration of OADs relative to meals, all of which are believed to be common during Ramadan [27–29].

There are some promising data on the efficacy and safety of DPP-4 inhibitors and GLP-1 analogs of the incretin class during Ramadan, although results have not always been entirely consistent. One analysis of 16 published studies concluded that there was some evidence that DPP-4 inhibitors led to fewer episodes of hypoglycemia than sulfonylureas. The analysis, while only analyzing one trial with a GLP-1 analog, indicated that GLP-1 analogs also provide clinical benefits during Ramadan compared with sulfonylureas [30]. Schweizer et al. [31] also concluded that DPP-4 inhibitors may be safe and effective, but a pooled analysis of data from three randomized controlled trials (RCTs) suggested that sulfonylureas had similar incidence of hypoglycemic episodes compared to DPP-4 inhibitors during Ramadan [32].

Compared to DPP-4 inhibitors, there is less information regarding the use of GLP-1 analogs in T2D during Ramadan, with only two trials currently published. One RCT reported a greater proportion of subjects achieving the composite end point of glycated hemoglobin (HbA_{1c}) <7.0% and weight loss with no severe hypoglycemic events for liraglutide compared to sulfonylureas (both in combination with metformin) [33]. Another RCT has demonstrated fewer hypoglycemic episodes with equivalent glycemic control and greater body weight reduction for liraglutide versus sulfonylurea (both in combination with metformin) [34]. With regard to comparisons of the two classes of incretin drugs, there are currently no trials comparing DPP-4 inhibitors and GLP-1 analogs directly during Ramadan.

Choosing the optimal treatment for patients with T2D requires a robust evidence base; but at least quantitatively, the volume of evidence from clinical trials during Ramadan fasting is

much more limited than that for the general population of people with T2D. Furthermore, the quality of the available information, as well as what might be needed to establish a more reliable evidence base, is not clear, and some results appear to be contradictory. Therefore, we conducted this review to critically examine published evidence from both RCTs and observational studies in T2D during Ramadan, with the goal of summarizing the degree to which they are consistent in key areas of trial design. An additional goal was to assess the comparability of results across trials and identify inconsistencies or deficiencies that should be addressed in the design of future studies. Thus, given our emphasis on understanding the important contribution of trial design to the evidence base, efficacy and safety results per se from individual trials will not be discussed in detail here.

METHODS

PubMed was searched for the terms "Ramadan" and "diabetes" in either the title or abstract from 1980 to the present. In total, 197 citations were retrieved. Abstracts were reviewed, and papers describing either randomized trials or observational studies of non-insulin treatments in T2D during Ramadan and reporting efficacy and/or safety were retained. In addition, the bibliographies of retrieved papers were manually searched to identify any additional relevant studies. The retrieved studies were characterized with respect to key aspects of study design and methodology (e.g., populations, OAD treatments used, duration of trial and period of assessment, choice of end points and measurement of those end points) that are particularly pertinent to the unique aspects of trials of diabetes treatments during religious fasting, as well as the consistency and completeness of reporting of these features.

This article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

RESULTS

Design and Methodological Characteristics of Studies

The key features of study design are presented in Table 1 for 10 RCTs and in Table 2 for 20 observational studies.

Treatments Studied

Sulfonylureas and drugs of the incretin class appear to be the most widely studied non-insulin treatments in comparative trials during Ramadan. However, individual RCTs sometimes did not differentiate among the different sulfonylureas used by patients, simply grouping different sulfonylureas (e.g., gliclazide, glibenclamide, glimepiride; glipizide) together as a class when reporting results (Table 1). This may not be appropriate, as these drugs have durations of actions of 12–18 h, 12–16 h, 12–24 h, and 6–10 h, respectively [35]. In addition, pooled data from a number of agents in the sulfonylurea class mask the different hypoglycemia risks associated with the individual drugs, as newer generation sulfonylureas such as gliclazide are associated with a lower hypoglycemia risk compared with other sulfonylureas [36]. In fact, a meta-analysis showed no difference in hypoglycemia incidence with gliclazide compared with DPP-4 inhibitors [37]. By contrast, results for drugs of the incretin class

Table 1 Randomized clinical trials involving Muslim patients with type 2 diabetes during Ramadan

Study	Country	Treatment	Number of patients [sample size calculation reported]	Primary end point(s)	Hypoglycemia definition	Run-in period	Follow-up after Ramadan	Blinding	QoL assessed	Adherence to fasting	Gender differences reported
Azar et al. [34], abstract	Unknown	Liraglutide + met vs. sulfonylurea + met	343 [no]	Change in fructosamine from the start of Ramadan to end	Subject unable to treat themselves and/or plasma glucose <3.1 mmol/L with or without symptoms	9–22 weeks	Not specified	Open label	No	Not described	No
Brady et al. [33]	UK	Liraglutide + met vs. sulfonylurea (gliclazide, glimepiride, or glibenclamide) + met	99 [yes]	Composite: HbA_{1c} <7.0%, wt loss or weight gain <1 kg, no severe hypoglycemic events at 12 weeks	SMBG ≤3.9 mmol/L	14 days for liraglutide, 2–4 weeks for sulfonylurea	3 weeks post, 12 weeks post	Open label	Treatment satisfaction	Not described	Not reported
Hassanein et al. [36]	16 countries in Middle East, Europe, Asia	Vildagliptin + met vs. sulfonylurea (gliclazide) + met	557 [no]	Proportion of patients experiencing at least one hypoglycemic event during Ramadan fasting	Symptoms ± SMBG <3.9 mmol/L and/or SMBG <3.9 mmol/L	At least 8 weeks	≤4 weeks post	Double-blind, double-dummy	No	Mean days fasting 28.3 ± 3.0 28.1 ± 3.8	Not reported
Malha et al. [39]	Lebanon	Vildagliptin + met vs. sulfonylurea (gliclazide or glimepiride) + met	69 [no]	Number of hypoglycemic episodes before and during Ramadan	SMBG <3.9 mmol/L or symptoms	Unclear: visits at baseline and prior to Ramadan were listed	End Ramadan 4 weeks post	Open label	No	Eight patients listed as breaking fast	Not reported
Abid [45]	Azad Kashmir, Pakistan	Sitagliptin + met vs. sulfonylurea (glimepiride)	64 [yes]	Hypoglycemia	Unclear	1 month	3 months post	Open label	No	Not described	Not reported
Aravind et al. [46]	India and Malaysia	Sitagliptin ± met vs. sulfonylurea (gliclazide, glimepiride, or glibenclamide) ± met	870 [no]	Proportion of patients reporting at least one symptomatic hypoglycemic event during Ramadan	Symptoms	Unclear	End Ramadan	Open label	No	Percentage of patients not breaking fast[a] 98.4% and 97.2%	Not reported

Table 1 continued

Study	Country	Treatment	Number of patients [sample size calculation reported]	Primary end point(s)	Hypoglycemia definition	Run-in period	Follow-up after Ramadan	Blinding	QoL assessed	Adherence to fasting	Gender differences reported
Al Sifri et al. [47]	Egypt, Israel, Jordan, Lebanon, Saudi Arabia and the United Arab Emirates	Sitagliptin ± met vs. sulfonylurea (gliclazide, glimepiride, or glibenclamide) ± met	1066 [yes]	Overall incidence of symptomatic hypoglycemic events during Ramadan	Symptoms	Unclear	End Ramadan 2 weeks post	Open label	No	Percentage of patients not breaking fast[a] 93.7% and 89.7%	Not reported
Anwar et al. [49]	Malaysia	Repaglinide vs. sulfonylurea (glimepiride)	41 [yes]	Glycemic control from weekly 4-point SMBG during and after Ramadan	BG <3.1 mmol/L	3 months	Weekly for 4 weeks post	Open label	No	Not described	Not reported
Vasan et al. [48]	India	Pioglitazone + OADs vs. placebo + OADs	87 [yes]	Number of hypoglycemic events during Ramadan, glycemic control	Symptoms only	74 days for conventional OADs	2 weeks post End of study (not specified)	Double-blind	No	Not described	Not reported
Mafauzy [50]	Malaysia, UK, France, Saudi Arabia, Morocco	Repaglinide vs. sulfonylurea (glibenclamide)	235 [yes]	Serum fructosamine	SMBG < 2.8 mmol/L or symptoms with SMBG ≥ 2.8 mmol/L	6 weeks	End Ramadan Final visit (not specified)	Open label	No	Not described	Not reported

HbA_{1c} glycated hemoglobin, *met* metformin, *OAD* oral antidiabetic drug, *SMBG* self-measured blood glucose, *wt* weight

[a] Percent of patients not breaking fast except due to hypoglycemia

Table 2 Observational studies involving Muslim patients with type 2 diabetes during Ramadan

Study	Country	Treatment	Number of patients [sample size calculation reported]	Primary end point(s)	Hypoglycemia definition[b]	Follow-up after Ramadan	QoL assessed	Adherence to fasting	Gender differences reported
Siaw et al. [57]	Singapore	OADs and/or mealtime or basal insulin	153 [no]	HbA_{1c} before, during and after Ramadan	Symptoms	Post-Ramadan	No	Mean days fasting 26 days	Not reported
Al-Arouj et al. [40]	Bangladesh, Egypt, India, Indonesia, Kuwait, Lebanon, Oman, Pakistan, Saudi Arabia and the United Arab Emirates	Vildagliptin ± met vs. sulfonylurea (gliclazide, glimepiride, glibenclamide or glipizide) ± met	1333 [no]	The proportion of patients with ≥1 hypoglycemic event during fasting	Symptoms and/or SMBG <3.9 mmol/L, or third-party assistance	≤6 weeks post	No	Mean days fasting 28.5 ± 3.9 28.6 ± 3.3	Not reported
Halimi et al. [41]	France	Vildagliptin + met vs. secretagogue (sulfonylurea or glinide) + met	198 [somewhat]	The incidence of all hypoglycemic events during Ramadan	Symptoms, SMBG ≤3.9 mmol/L, or third-party assistance	6 weeks post	No	Patients who interrupted fast ≥1 day 25.6% and 21.7%	Not reported
Karatoprak et al. [53]	Turkey	OADs and/or insulin	147 [no]	Comparison of efficacy and safety end points in fasting vs. non-fasting patients	Mild: 2.8–3.9 mmol/L Severe: <2.8 mmol/L	15 days post	No	Fasting group fasted a mean of 16.5 h/day	Not reported
Sahin et al. [56]	Turkey	OADs alone OADs + insulin Insulin alone	122 [no]	Glycemic control and acute complications during Ramadan	Symptoms urging patient to break the fast ± SMBG (cutoff not specified)	≤2 weeks post	Lifestyle changes	$N = 88$ (72.1%) fasted for a mean of 27 ± 6 days 71.6% fasted 30 days and 89.8% fasted ≥15 days	Not reported
Shete et al. [42]	India	Vildagliptin ± met vs. sulfonylurea (gliclazide, glimepiride, glibenclamide or glipizide) ± met	97 [yes]	Incidence of hypoglycemic events during the study period	Symptoms confirmed by BG <3.9 mmol/L	≤10 days post	No	100% fasted 29 days	Not reported
Lessan et al. [54]	United Arab Emirates	Lifestyle ± OADs ± insulin or ± incretins	23 [no]	Changes in BG profiles as measured using CGM	Symptoms or CGM ≤3.9 mmol/L	3 consecutive days during	No	Not described	Not reported
Norouzy et al. [55]	Iran	Lifestyle ± OADS (sulfonylurea and/or met)	88 [yes]	Fasting BG, fasting insulin, HbA_{1c}, fasting lipids	Not discussed	3 days post 1 month post	No	Mean days fasting 25.2 ± 0.7 and a mean of 14 h/day	Not reported
Aravind et al. [60]	India, Malaysia, Israel, the United Arab Emirates, and Saudi Arabia	Sulfonylurea (gliclazide, glimepiride, or glibenclamide) ± met	1378 [no]	Incidence of symptomatic hypoglycemic events during Ramadan	Symptoms	End of Ramadan	No	89% fasted	Not reported

Table 2 continued

Study	Country	Treatment	Number of patients [sample size calculation reported]	Primary end point(s)	Hypoglycemia definition[b]	Follow-up after Ramadan	QoL assessed	Adherence to fasting	Gender differences reported
Bonakdaran et al. [61]	Iran	Metformin, sulfonylureas or both	17 [no]	Excursions during 72 h of CGM after 15 consecutive days of fasting	Glucose value <3.88 mmol/L ± symptoms	N/A	No	Not described	Not reported
Hassanein et al. [43]	UK	Vildagliptin + met vs. sulfonylurea (gliclazide) met	72 [yes]	Proportion of patients who experienced ≥1 hypoglycemic event	Symptoms ± BG <3.9 mmol/L, or third-party assistance	≤6 weeks post	No	Mean days fasting 25.0 ± 6.6 and 25.4 ± 5.8 days	Not reported
Elmehdawi et al. [52]	Libya	Diet, OADs, insulin	493 [no]	Frequency of fasting and incidence of complications during Ramadan	Symptoms urging patient to break the fast ± SMBG, or third-party assistance	N/A (medical record review)	No	66.9% of females and 73.8% of males fasted entire month 95.6% of females and 99.6% of males fasted ≥15 days Mean fasting days 28.5 ± 4.6	Females had a significantly higher frequency of severe hypoglycemic episodes (4.9% vs. 1.6%, $P = 0.04$) and a lower mean number of fasting days than males (27.8 ± 5.9 vs. 29.24 ± 2.6, $P = 0.001$)
Zargar et al. [29]	India, Bangladesh, Pakistan	Sulfonylurea (gliclazide)	136 [no]	Difference in FPG before and after Ramadan	Symptoms	End of Ramadan Final visit	No	Not described	N/A (only males studied)
Ahmadani et al. [51][a]	Pakistan	Diet, OADs, insulin	453 [no]	Hypoglycemia and hyperglycemia before and during Ramadan	Symptoms	Retrospective questionnaire	No	96.3% of patients with T2D fasted for a mean of 25 days	Not reported
Devendra et al. [44]	UK	Vildagliptin + met vs. sulfonylurea (gliclazide) + met	52 [no]	Hypoglycemic events, HbA_{1c}, and weight change	Symptoms ± BG <3.5 mmol/L	10 days post	No	Mean days fasting 20.4 ± 2.7 and 21.6 ± 3.0 days	Not reported
Cesur et al. [62]	Turkey	Fasting vs. non-fasting patients, all using one of the below: Sulfonylurea (glimepiride) + met, repaglinide + met, or insulin + met	49 16 [no]	To compare the effects of the three treatments on glucose metabolism	Symptoms and/or SMBG <3.9 mmol/L	Weekly phone interviews during Ramadan	No	Duration of fasting for fasting group not reported	Not reported
GLIRA Study Group [59]	Algeria, Egypt, Indonesia, Jordan, Lebanon, and Malaysia	Sulfonylurea (glimepiride)	332 [no]	HbA_{1c} and FBG	Symptoms and/or SMBG <3.9 mmol/L	End of Ramadan 45–75 days post	No	Not described	Not reported

Table 2 continued

Study	Country	Treatment	Number of patients [sample size calculation reported]	Primary end point(s)	Hypoglycemia definition[b]	Follow-up after Ramadan	QoL assessed	Adherence to fasting	Gender differences reported
Sari et al. [63]	Turkey	Diet only, sulfonylurea (glimepiride, gliclazide), or repaglinide	52 [no]	FBG, PPG, fasting plasma fructosamine, HbA_{1c}, lipids and beta-hydroxybutyric acid	Symptoms and/or documented BG (cutoff not specified)	Post-Ramadan	No	Not described	Not reported
Uysal et al. [58]	Turkey	Diet ± OADs	41 [no]	Episodes of hypoglycemia, HbA_{1c}, lipid profiles	Symptoms, reviewed by a physician	Post-Ramadan	No	Not described	Not reported
Belkhadir et al. [77]	Morocco	Fasting vs. non-fasting patients, using sulfonylurea (glibenclamide)	542 [yes]	Serum fructosamine, HbA_{1c}, number of hypoglycemic events before and after fasting as well as between fasting and non-fasting groups	Symptoms, reviewed by a physician	End Ramadan ~5 weeks post	No	Not described	Not reported

BG blood glucose, *CGM* continuous glucose monitoring, *FBG* fasting blood glucose, *FPG* fasting plasma glucose, *HbA1c* glycated hemoglobin, *met* metformin, *N/A* not applicable, *OAD* oral antidiabetic drug, *SMBG* self-monitored blood glucose, *T2D* type 2 diabetes

[a] Study included both type 1 and T2D, but only 3.7% of patients with type 1 diabetes fasted vs. 96.3% of patients with T2D

[b] When hypoglycemia was used as the primary end point, definition of hypoglycemia used for secondary or safety end points not included

have been reported individually for vildagliptin (two RCTs [38, 39] and five observational studies [40–44]) for sitagliptin (three RCTs [45–47]) and liraglutide (two RCTs [33, 34]). The use of metformin was common, but not universal (Table 1). Both RCTs using liraglutide included metformin [33, 34], as did the two studies using vildagliptin [38, 39] and one of three RCTs using sitagliptin [45]. However, metformin was optional for two of the RCTs using sitagliptin [46, 47] and one trial using pioglitazone [48]. Metformin was not used in the two trials examining repaglinide [49, 50].

Treatments used in the observational studies were quite heterogeneous, with some studies even combining patients using various combinations of OADs and/or insulin and/or diet alone into a single group [51–57] (Table 2).

Eligibility, Number, and Comparability of Patients

In the RCTs, the number of subjects varied from 41 to 1066. Inclusion and exclusion criteria were mentioned in some way for all RCTs, but the level of details presented varied greatly. All of the RCTs described prior diabetes treatments, and most of the trials enrolled subjects previously treated with metformin or sulfonylurea either as monotherapy or in combination. However, in a few trials, a minority of patients had been treated with thiazolidinediones, glinides, or acarbose (Table 1). A specific cutoff for glycemic control (HbA_{1c}) for eligibility was only specified for four RCTs (7–10% [34]; 6.5–12.0% [33]; ≤8.5% [38]; ≤10% [46, 47]). One trial indicated that participants had to be "well controlled" [45]. Most ($n = 7/10$) trials excluded patients with a history of recurrent hypoglycemia, severe hypoglycemia, or hypoglycemia unawareness [33, 45–48, 50], but others made no such exception [38, 39, 49]. Exclusion of patients with at least some serious systemic diseases was reported in all but three trials, but the level of stringency reported varied [39, 47, 49].

There was also a considerable range in the number of patients participating in the observational studies (23–1333 patients; Table 2). With the exception of four reports [54–56, 58], all of the observational studies mentioned patient inclusion/exclusion criteria to some extent. However, as with RCTs, the stringency of these criteria varied considerably among studies. For example, some studies indicated that all patients with T2D were included [51] or that all consecutive patients were enrolled [52], whereas others specified more detailed inclusion criteria such as age, type of prior treatment, and/or willingness to fast. Most studies did not specify any HbA_{1c} cutoff for eligibility, although one required HbA_{1c} ≤9.0% [29], two required HbA_{1c} ≤8.5% [40, 43], one required HbA_{1c} ≤8.0% [41], and one just indicated that patients had to be in "good control" [59].

The same variation was noted with respect to exclusion criteria, with some observational studies indicating no exclusion criteria other than insulin treatment (e.g., [44, 60]) and others listing very specific exclusion criteria (e.g., duration of diabetes, level of glycemic control, prior treatments, incomplete fasting, incomplete medical records, and/or serious renal, hepatic, cerebrovascular or cardiovascular disease, pregnancy or lactation; retinopathy, and uncontrolled hypertension [29, 40, 41, 53, 61, 62]). In contrast to the RCTs, few observational studies mentioned excluding patients with severe hypoglycemia [57], recurrent hypoglycemia [61, 62], or hypoglycemia unawareness [63], but otherwise this appeared uncommon. One study using continuous glucose monitoring (CGM)

indicated that "low-risk" patients were enrolled [61].

Choice and Measurement of End Points

The critical factor of end points was not consistent across studies, either with respect to the choice or efficacy or safety as a primary end point, or how those end points were measured. Three RCTs used a primary efficacy end point [34, 49, 50] and four RCTs indicated that the primary end point was a safety end point [38, 45–47], and in two, a primary end point was not explicitly stated or clear, with multiple efficacy and safety end points being listed [39, 48]. In one trial, a specific composite end point was used [33] (Table 1). In some studies where efficacy was indicated to be the primary end point, safety end points were also included. Conversely, in some studies where safety was listed as the primary end point, some efficacy measures were also reported.

When glycemic efficacy end points were reported, there were also considerable differences in how they were measured, ranging from CGM to self-monitored blood glucose (SMBG), to clinic visits with laboratory measures, to patient diaries with or without review by a physician, to phone interviews and retrospective review of medical records. Secondary end points such as weight change, blood pressure, lipids, and quality of life were inconsistently reported.

Definition of Safety (Hypoglycemia) Outcomes

In the RCTs, the definition of hypoglycemia, as well as how hypoglycemia was measured, varied. Two trials used symptoms only [47, 50]. When a cutoff value was mentioned, most trials specified a value of <3.9 or ≤3.9 mmol/L, although two trials utilized other values (<3.1 mmol/L [49] and <2.8 mmol/L [50]; Table 1). In one trial, the cutoff point was unclear [45]. There were also cases where a primary end point used symptoms as the criteria, but the results for additional hypoglycemic end points were also reported (e.g., [46, 47]).

There was also considerable variability in how hypoglycemia was defined and measured in the observational studies (Table 2). Some studies used patient-reported symptoms only [29, 51, 57, 60], but more typically used symptoms with or without blood glucose (BG) measurements [40, 41, 43, 44, 52, 56, 62]. In one of these cases, the cutoff was not specified [56]. The BG cutoff values used were also heterogeneous (<3.9 mmol/L [40]; ≤3.9 mmol/L [41]; 2.8–3.9 mmol/L [53]; <3.9 mmol/L [42]; <3.88 mmol/L [61]; <3.9 mmol/L [43]; <3.5 mmol/L [44]).

Duration of Treatment and Follow-Up

There was great variation in the amount of time patients were assessed, treated, and followed across studies. In the RCTs (Table 1), the run-in period for the non-sulfonylurea treatment varied considerably, even where patients were switching to the identical drug. For example, Anwar et al. [49] reported a 3-month run-in period for patients switching to repaglinide, whereas Mafauzy [50] reported 6 weeks. For three trials using incretins, one with vildagliptin [39] and two with sitagliptin [46, 47], the duration of the run-in period was unclear. The duration of follow-up post-Ramadan, when fasting ceased and normal diet and lifestyle patterns resumed, was also variable and sometimes difficult to discern. For the observational studies (Table 2), there was also great variation in the length of

time during which patients were assessed and data obtained.

Blinding Protocols

Blinding of subjects and evaluators during a clinical trial is considered an important protection against bias. Of the 10 RCTs, only two trials were blinded [38, 48] (Table 1). One was a double-blind, double-dummy trial [38], and the other was double-blinded [48]. By definition, blinding was not possible in the observational studies.

Definition and Characteristics of Fasting

Fasting was not always explicitly defined in studies. In the RCTs, the intent to fast was either stated or assumed based on screening criteria in nine out of ten trials, but only one trial indicated a specific minimum amount of time (i.e., at least 10 days) for fasting [33]. One trial indicated that participants would be excluded if they expected to break their fast for >3 days [50]. It has been reported that the ability to keep a fast may also depend on the type of treatment [64], but this was not regularly reported and, when reported, not in sufficient detail to allow for meaningful interpretation of the likely impact of non-adherence on treatment. Adherence to fasting was not described for six RCTs [33, 34, 45, 48–50]. When adherence was reported, the statistic used varied (Table 1). For example, one study reported the mean number of days of fasting for the two treatment groups (i.e., 28.3 ± 3.0 and 28.1 ± 3.8 days) [38], whereas two other trials reported the proportion of people in each treatment group who did not break their fast except to treat symptoms of hypoglycemia (i.e., 89.7% to 98.4% of participants) [46, 47]. It was often unclear what constituted an interruption of fasting, whether an interruption was temporary or permanent, or under what circumstances an interruption might be of sufficient duration to be considered a break in the fast (non-adherence). For example, one RCT indicated that eight individuals in one of the treatment arms broke their fast, but did not quantify or otherwise describe what that meant [39].

In the observational studies, intention to fast (or actual fasting) during Ramadan was either an implicit or explicit inclusion criteria. In some cases, the period of intending to fast was pre-specified in some detail (>10 days [43, 55, 57]; ≥15 days [61]; ≥20 days [61]; or throughout Ramadan [59, 62]). In general, there was more attention to describing adherence to fasting in the observational studies, with 13/20 studies reporting some measure of adherence (Table 2). This was most frequently framed as the mean number of days of fasting. However, an inspection of these mean values in the table (e.g., from approximately 20.4 to 28.6 days) makes it clear that some participants did not fast the entire month of Ramadan.

Ramadan-focused Education and Quality of Life Assessment

The potential value of patient education has been evaluated in a number of clinical studies. For example, patients with T2D using OADs who received a Ramadan-focused education and awareness in diabetes (READ) program demonstrated a decrease in hypoglycemic episodes during Ramadan [65]. Another comparative trial in Thailand showed that patients in the group receiving education prior to Ramadan significantly reduced the number of hypoglycemic episodes ($P = 0.013$), diastolic blood pressure, ($P = 0.041$), and consumption

of sweetened food ($P = 0.002$), and the number of patients with hypoglycemic symptoms was also lower ($P = 0.013$) [66]. A comparison of patients recruited from clinics in four Muslim nations who received an individualized educational program vs. those who did not showed significant improvements in a variety of diabetes management outcomes, such as modifying their treatment plan ($P < 0.001$), performing SMBG at least twice daily ($P < 0.0001$), and having improved knowledge about hypoglycemic signs and symptoms ($P = 0.0007$), as well as fewer severe hypoglycemic events ($P = 0.0017$) [67]. One uncontrolled study described the practicality of implementing a Ramadan-specific educational program through diabetes-specialist centers [68]. The study reported that drug dose and timing were modified in 90.5% of patients with T2D.

The extent to which Ramadan-focused education is included in trials whose primary goal is to compare drug treatment regimens is unclear. Among the randomized trials summarized in Table 1, only one study explicitly mentioned providing Ramadan-focused education, which was given to patients in both arms of the trial [38]. However, two other trials mentioned providing medical counseling regarding risks of hypoglycemia during fasting [46, 47]. It is unclear to what degree these issues may have been raised during the routine informed consent process in other trials. Among the observational studies (Table 2), three mentioned providing Ramadan-focused advice about diabetes management [42, 44] or information about the risks associated with fasting [62], again provided to all patients participating in the studies. Future trials should explicitly include and describe the extent of Ramadan-focused education for participants.

With regard to patient-reported outcomes and quality of life assessment, only one of the reviewed studies assessed treatment satisfaction and one assessed lifestyle changes [56, 69].

Reporting of Diet and Exercise

Changes in diet and exercise were reported infrequently, and when reported, typically, this was not in sufficient detail to enable adequate account for confounding effects of these changes when evaluating the efficacy and/or safety of the treatments being studied. Only one RCT provided such data, with physical activity assessed by the International Physical Activity Questionnaire (IPAQ), and diet information reported in the form of changes in score for total Metabolic Equivalent Tasks (METS) for each treatment group [33].

Among the observational studies, as with the RCTs, reporting of data on diet and exercise was very limited, with only 3/20 studies providing information. Siaw et al. [57] reported general trends in diet and exercise during Ramadan, describing these only as "more," "less," or "unchanged". An analysis of the proportion of patients reporting reduction (64.7%), increase (5.9%), or no changes (29.4%) in dietary intake, as well as data on physical exercise, indicated that there were no significant associations between these categories and improvements in mean HbA_{1c} during fasting. Sahin et al. [56] also reported similar categorical groupings of changes in diet and exercise, whereas Ahmadani et al. [51] reported caloric intake for 1 day before and after fasting, in addition to a simple dichotomous outcome of diet having changed or not and exercise having changed or not. In some cases when it was mentioned in the Methods section of a paper that information

on diet and/or exercise was obtained from patients, the results for those variables were not presented in the trial report. For example, Bonakdaran et al. [61] indicated that patients were required to record dietary programs, time of meals, quality and quantity of meals, and time and extent of exercise, but those data were neither reported nor apparently factored into the analysis of BG readings or hypoglycemic events. Zargar et al. [29] also mentioned that data on meals were obtained, but no results were presented.

Classes of Diabetes Treatments Studied

The 10 RCTs were heterogeneous with respect to diabetes treatments evaluated, with five comparing sulfonylureas to DPP-4 inhibitors, two comparing sulfonylureas to GLP-1 analogs, two comparing sulfonylurea to repaglinide, and one comparing sulfonylurea to pioglitazone (Table 1). In some cases, only one sulfonylurea was used, and in others, a variety of sulfonylureas was permissible. Use of metformin was inconsistent, with some trials allowing it, others mandating it, and others excluding metformin. No RCTs have compared receptor GLP-1 receptor agonists and DPP-4 inhibitors head-to-head in the treatment of T2D during Ramadan. This is in contrast to at least seven such studies published in patients with T2D not focused on Ramadan fasting (see [70]). Being a more recently introduced class of drugs, sodium-glucose co-transporter 2 inhibitors have not yet been studied in fasting patients with T2D during Ramadan.

Observational studies were even more heterogeneous with respect to the treatments studied and it was not uncommon to group together patients using treatments ranging from lifestyle management to OADs to insulin, either individually or in combination (Table 2).

Adherence to Treatment

In the RCTs, adherence to treatment was difficult to discern. One RCT reported the proportion of missed doses [38], and others reported the proportion of patients who changed the dose or timing of their medication [46, 47]. One study reported the proportion of completers reaching the optimal dose [49], and another reported the proportion of patients exposed to treatment for >6 and >10 weeks [50].

Limited reporting of adherence to treatment was also typical in the observational studies. When mentioned (6/20 studies), this was usually brief and in the form of proportion of patients with missed doses, proportion making adjustments to dose, or changes in the timing of dose (e.g., [43, 51, 54, 56, 57, 60]). Few studies provided detailed measures of adherence (e.g., overall adherence per treatment group, proportion of patients with treatment change in each group, type of treatment change, number of times the treatment was not taken, and/or number of times the treatment was not taken due to hypoglycemia or fear of hypoglycemia) [40, 41]. Across these studies, analysis of how these various measures of adherence to each treatment were related to the frequency of hypoglycemic events was generally lacking.

DISCUSSION

The studies reviewed here, conducted in populations of Muslims with T2D who fasted during Ramadan, were quite heterogeneous in critical components of their design, including but not limited to patient eligibility and exclusion criteria, glucose control and treatments at entry, choice of outcomes assessed and definitions of those outcomes,

and method and timing of outcomes assessment, all of which significantly limit the ability to compare results across trials. This was true for RCTs as well as for the observational studies. Compared with typical diabetes trials in non-Muslim/non-fasting patients, there appears to be a trend for trials during Ramadan to emphasize safety end points over efficacy end points. The choice of either an efficacy or safety measure as the primary end point also has bearing, because a primary end point may be used for power calculation, which may result in a study being underpowered to capture other end points. Efficacy and safety should be included in the reporting of data, so that comprehensive information is made available to clinicians to support clinical decision making.

With respect to efficacy, the choice of end point and measurement method should be aligned with the duration of the trial and follow-up period. HbA_{1c} is the standard efficacy end point used in the majority of longer duration clinical trials and can be reliably and easily measured. HbA_{1c} reflects glycemia over the lifespan of red blood cells, but predominantly glycemia during 6–8 weeks prior to the time of measurement. This is a period substantially longer than the duration of fasting during Ramadan. By comparison, fructosamine has the ability to assess glycemic control during shorter periods of assessment compared to HbA_{1c}, as it reflects average glycemia the preceding 1–3 weeks [71, 72]. Although fructosamine is not widely used in clinical trials, it has been used as the primary end point in a recent RCT with liraglutide, so clinicians may become more familiar and comfortable using it [34]. Another validated short-term marker for glycemic control, especially for recent postprandial hyperglycemic excursions and glycemic variability, is 1,5-anhydroglucitol [73, 74]. Ambulatory glucose monitoring and CGM offer the possibility of very precise characterization of daily blood glucose excursions and allows the possibility of assessing those changes in light of changes in diet. The choice of CGM as a tool will need to be balanced against the increased cost and complexity associated with its use.

With respect to safety, one obvious concern for patients with T2D taking glucose-lowering medications during fasting is the risk of hypoglycemia. Having a precise, accurate, and uniform method of assessing hypoglycemia, as well as clearly defined cut points, is important for being able to evaluate trial results and to compare across trials. Similar entry criteria with respect to history of hypoglycemia or hypoglycemia unawareness are essential for comparing the results of different studies.

Understanding diet and exercise patterns associated with diabetes treatment is particularly important for trials conducted during Ramadan, given that prolonged fasting involves major changes in routine eating habits and/or the timing of exercise that may affect glycemic control. Few of the studies summarized here reported any diet and exercise outcomes, and those that did categorized diet and exercise patterns very fundamentally (e.g., as increased, decreased, unchanged) [56, 57]. Such an approach may be overly simplistic and not capture important features of changes in diet or exercise. Furthermore, use of a limited number of discreet categories would tend to render any adjustment for confounding by those factors imprecise, although it should be noted that such an adjustment was not reported in any of the trials. How to best assess and control for changes in diet when the frequency, content,

and volume of meals may change substantially over the study period is an unanswered question. Thorough dietary assessment involves techniques such as 24-h recall and food frequency questionnaires (e.g., [75]), which may be cumbersome to add to a conventional trial already assessing efficacy and safety measures.

Adherence to fasting and duration of the actual fast are important to determine when studying the effects of treatment on glucose control. As noted in several studies, patient-initiated changes in medication timing or dose, or discontinuation of treatment during Ramadan, is common [28, 29]. However, adherence to treatment was often not reported, and when reported was typically not assessed relative to the outcome of interest, regardless of whether efficacy and/or safety measures were used. It is also critical to differentiate a stated intention to fast (which is typically a criterion for enrollment in a RCT) versus the actual fasting behavior during Ramadan. For example, the EPIDAIR study reported that the proportion of subjects fasting $\geq$15 days ranged from 57.8% in Turkey to 89.8% in Malaysia and Bangladesh [1]. It is sometimes mentioned that participants may periodically interrupt their fast temporarily if symptoms of hypoglycemia are experienced, but the duration of the interruption may not be specified [68]. As reviewed here, at the time of enrollment/screening, some patients may indicate an intention to fast throughout the entire month of Ramadan, whereas others may indicate fasting may not last the entire month. With respect to adherence, the actual duration of fasting may vary from the stated intention and be considerably less than the full month of Ramadan.

CONCLUSIONS

In part due to the degree of heterogeneity in key aspects of the study design from both RCTs and observational studies, comparability across studies remains difficult. Thus, the ideal treatment regimen for patients with T2D during Ramadan has not yet been identified. Given the unique challenges of managing diabetes during fasting, desirable characteristics of any treatment might include flexibility in timing of administration and/or once-daily dosing (so as not to conflict with prohibitions during the daytime hours when taking medications is not possible due to religious concerns), and a low risk of hypoglycemia (to better accommodate the prolonged period of fasting each day).

More definitive trials during Ramadan fasting, using more evolved trial designs (e.g., [34]), are needed to answer important clinical questions. Trials should include data on a full range of important clinical end points (e.g., glycemic control, hypoglycemia, hyperglycemia, other adverse events, lipid levels, blood pressure) and quality of life, and use clearly defined measures that are appropriate to these end points and time frame. Detailed assessment of potentially confounding variables such as changes in diet and exercise are also required so that appropriate adjustment for these factors can be performed when assessing outcomes. Ideally, some trials should also involve head-to-head comparisons between DPP-4 inhibitors and GLP-1 analogs. Despite the limitations of many published studies, there is evidence suggesting that newer drugs having a lower risk of hypoglycemia (such as those of the incretin class) may be beneficial for patients who choose to fast during Ramadan [30, 31, 34, 76].

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