ORIGINAL ARTICLE

Effect of Ramadan fasting in patients with type 2 diabetes mellitus treated with sodium–glucose cotransporter 2 inhibitors: A systematic review and meta-analysis

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ABSTRACT

Aims/Introduction: Sodium–glucose cotransporter 2 inhibitors (SGLT-2i) improve glycemic control and weight, but might be associated with dehydration, hypotension and ketoacidosis, especially in patients with type 2 diabetes mellitus who fast during Ramadan. This meta-analysis evaluates the effects of Ramadan fasting on patients with type 2 diabetes mellitus treated with SGLT-2i.

Materials and Methods: A literature search was carried out in PubMed, Embase and the Cochrane Library. Quality assessment was carried out using the ROBINS-I and Cochrane tools for risk of bias, and analyses were carried out using RevMan version 5.3.

Results: A total of five studies were included in this meta-analysis. During Ramadan, there was a significant reduction in glycated hemoglobin ($P < 0.00001$) and diastolic blood pressure ($P = 0.006$), with a non-significant trend for a reduction in weight ($P = 0.44$) and systolic blood pressure ($P = 0.67$). The number and severity of hypoglycemic episodes was lower in patients with type 2 diabetes mellitus treated with SGLT-2i compared with sulfonylureas. There was no significant change in estimated glomerular filtration rate, β-hydroxybutyrate, bicarbonate or anion gap. However, we identified considerable heterogeneity among studies, and a lack of head-to-head studies with structured outcome reporting on the risks and benefits of SGLT-2i during Ramadan.

Conclusions: This systematic review and meta-analysis shows that patients with type 2 diabetes treated with SGLT2i's during Ramadan have an improvement in HbA1c, less hypoglycemia and no major adverse effects.

INTRODUCTION

The prevalence of diabetes is increasing globally, especially in the Muslim majority regions of the Middle East, North Africa and South-East Asia[1]. The majority of Muslims observe fasting during Ramadan which has multiple clinical and metabolic benefits[2–4], but can also be associated with complications, especially in relation to medication[5]. The Epidemiology of Diabetes and Ramadan (EPIDIAR)[6] study showed that 89% of patients with type 2 diabetes mellitus fasted during Ramadan, and it

was also associated with an increased incidence of severe hypoglycemia and hyperglycemia. More recently, the Multi-Country Retrospective Observational Study of the Management and Outcomes of Patients with Diabetes during Ramadan (CREED) study showed that 95% of patients with type 2 diabetes mellitus taking oral hypoglycemic agents fasted during Ramadan and it was also associated with an increased incidence of hypoglycemia[7]. Based on their mechanism of action, newer therapies, such as dipeptidyl peptidase-4 inhibitors, glucagon-like peptide 1 receptor agonists and sodium–glucose cotransporter 2 inhibitors (SGLT-2i), have a better safety profile, particularly in relation to hypoglycemia[5].

Three SGLT-2i (dapagliflozin, canagliflozin and empagliflozin) are currently approved as glucose-lowering agents in adults with type 2 diabetes mellitus[8,9]. They primarily inhibit glucose reabsorption in the proximal renal tubules[8,9] to improve glycemic control, reduce weight, lower blood pressure, and reduce adverse cardiovascular and renal outcomes[10]. However, they can also increase the risk of dehydration, genitourinary infections and euglycemic ketoacidosis[11]. Several small studies have assessed the efficacy and safety of SGLT-2i during Ramadan[12–16]. The present systematic review and meta-analysis provides a pooled estimate effect of the benefits and adverse effects of Ramadan fasting in patients with type 2 diabetes mellitus treated with SGLT-2i.

MATERIALS AND METHODS

The present systematic review and meta-analysis is reported in accordance with the PRISMA guidelines (Appendix S1). The review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 9 November 2017 (CRD42017078057).

Data sources and extraction

Three databases were chosen to search for this systematic review: PubMed, Embase (Ovid) and the Cochrane Library (CENTRAL). In the PubMed database and Cochrane Library; both MeSH subject headings and keywords were searched; in Embase, Emtree subject headings and keywords were utilized. Numerous terms were tested for relevance, and the final search strings for the three databases can be found below (Table S1). Article languages were limited to those in English, and no date restrictions were set. A segment of the gray literature was searched through the use of Dissertation and Theses (ProQuest) and Conference Proceedings Citation Index-Science (CPCI-S) from 1990 to present/Conference Proceedings Citation Index-Social Science & Humanities (CPCI-SSH) from 1990 to present (Web of Science). The databases were searched from inception to October 2020. Citations resulting from the searches were all compiled into an EndNote library where they were de-duplicated. Citations were then uploaded into Covidence systematic review software (Melbourne, Vic. Australia), where they were selected/deselected according to inclusion and exclusion criteria.

Study selection

After removal of duplicates, all citations were screened for relevance using the full citation, abstract and indexing terms, before excluding studies deemed as not relevant. Where there was a lack of consensus, a third author was consulted (RAM). Duplicates were removed, and the most recent and complete versions of the studies were reviewed for eligibility. Relevant studies were assessed by two reviewers (HG and NA) to assess eligibility according to the pre-specified inclusion and exclusion criteria. We included randomized controlled trials and observational studies of patients with diabetes who fasted during Ramadan. Literature reviews, systematic reviews, correspondence and newspaper articles were excluded. Studies were included if they reported on at least one of the following: glycated hemoglobin (HbA1c) (%), weight (kg), body mass index (kg/m^2), systolic/diastolic blood pressure (BP; mmHg), estimated glomerular filtration rate (eGFR; mL/min/1.73 m^2), hypoglycemia (number of patients with the event), diabetic ketoacidosis (DKA), urinary and genitourinary tract infections, and other adverse events experienced pre-, during or after Ramadan fasting. Studies were excluded if they reported on fasting for other religious or spiritual purposes. Full manuscripts of these potentially eligible citations were obtained. Two reviewers (HG and NA) made the final inclusion and exclusion decisions independently. In case of disagreement, a third reviewer (RAM) was consulted to resolve the conflicts. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses[17] flow chart was produced. A data extraction sheet was developed for extracting the data from each study. The data included clinical and demographic details of the patients, medication exposure, setting and outcomes. Data extraction and verification were carried out by three reviewers (HG, NA and IM).

Quality assessment

Included studies were assessed using the Risk of Bias In Non-randomized Studies – on Interventions (ROBINS-I) tool[18]. This tool categorizes the risk of bias as low, moderate, serious, critical and unclear. The Cochrane Collaboration's tool for assessing risk of bias was used for the randomized studies (section 8.5)[19]. This tool assessed six domains: selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias. Quality assessment was undertaken by one reviewer and checked by a second reviewer, and disagreements regarding the quality of a trial were resolved by consensus, or after consultation with the third reviewer (RAM). If a study's risk of bias was serious, critical or unclear, the effect of removing this study was checked and relevant outcomes were reported.

Statistical analysis

Meta-analysis was carried out in RevMan (version 5.3). Random effects meta-analysis was used in anticipation of heterogeneity due to differences in study design and population. Mean differences (MD) with 95% confidence intervals (CI) were calculated for the continuous variables: HbA1c, weight, BP and eGFR. Studies reporting variables as mean ± standard error were converted to the mean ± standard deviation using RevMan calculator for the purpose of homogeneity of the data and to build the forest plot. The I^2 statistic was calculated, which is derived from Cochrane's χ^2-test Q, and is used to describe the percentage of between-study variations attributable to variability in the true exposure effect. An I^2 value of 0–40% was classified as not important, 30–60% as moderate, 50–90% as substantial and 75–100% as considerable.

RESULTS

The search strategy identified 205 records (Figure 1). After removing duplicates, 184 papers were screened on the basis of their titles and abstracts, out of which 167 were excluded, resulting in 17 papers being assessed using their full text. After exclusions, five studies were included in the meta-analysis (Table 1).

Synthesis of results

HbA1c

Three studies[12–14] of 1,256 participants were included. There was a significant reduction in HbA1c (%) during/after Ramadan (MD = −0.43, 95% CI −0.56 to −0.31, $P < 0.00001$; Figure 2a).

Weight

Four studies[12–15] of 1,326 participants were included. There was a non-significant reduction in weight (kg) during Ramadan fasting (MD = −0.68, 95% CI −2.40 to 1.04, $P = 0.44$; Figure 2b).

Systolic BP

Three studies[12–15] of 492 participants were included. There was a non-significant reduction in systolic BP (mmHg) during/after Ramadan fasting (MD = −1.1, 95% CI −6.12 to 3.93, $P = 0.67$; Figure 2c).

Diastolic BP

Three studies[12–15] of 492 participants were included. Diastolic BP (DBP; mmHg) was reduced significantly during/after Ramadan compared with pre-Ramadan (MD = −1.95, 95% CI −3.33 to −0.57, $P = 0.006$; Figure 2d).

eGFR and serum creatinine

Three studies[12–15] of 492 participants were included. There was a non-significant (MD = −2.39, 95% CI −5.85 to 1.08, $P = 0.18$) reduction in eGFR (mL/min/1.73 m^2) during/after Ramadan (Figure 2e). Abdelgadir *et al.*[12] showed a non-significant reduction in serum creatinine after Ramadan fasting (0.8 ± 0.2 vs 0.7 ± 0.2 mg/dL, $P = 0.85$)[12], whereas Bashier *et al.* observed no change[13].
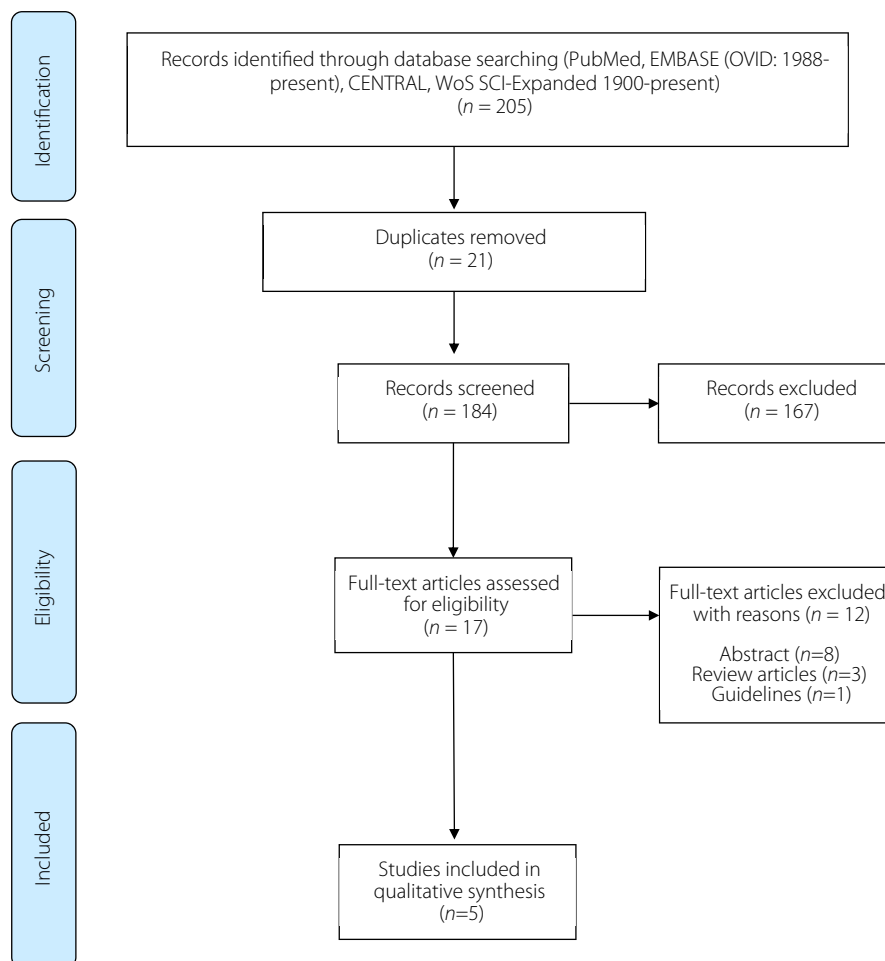

Figure 1 | PRISMA diagram of included studies.

Table 1 | Summary of the included studies

Methods

Study ID	Country	Total sample (n)	Age (years)	Hypoglycemia	Sex
Abdelgadir 2019	Dubai, UAE	49	Median ± SD 57.5 ± 9.1		Both
Bashier 2018	Dubai, UAE	417 (227 on SGLT-2 and OHA and 190 on SGLT-2 and insulin)	NS		Mostly females
WanSeman 2016	Malaysia	58	Median (IQR) 53 (9.1)		Both
Shao 2018	Singapore	35	Mean ± SD 49.9 ± 10.6		Both
Hassanein 2017	Middle East (Lebanon, Kuwait and the United Arab Emirates)	162	Mean ± SD 52.3 ± 7.7		Both

Study ID	HbA1c	weight	SBP	DBP	b-hydroxybutarate	eGFR	Creatinine	Hypoglycemia
Before Ramadan								
Abdelgadir 2019	7.95 ± 1.1	82 ± 13.9	131 ± 17.1	70 ± 10.6	NS	100.5 ± 21.4	0.8 ± 0.2	No. hypoglycemic events BR (n/sensor) 5 ± 6.9
Bashier 2018	8.3 ± 1.7	83.9 ± 17	NS	NS	NS	NS	NS	NS
WanSeman 2016	7.7 ± 0.44	NS	NS	NS	NS	NS	NS	NS
Shao 2018	9.3 ± 1.8	88.2 ± 24.1	137.7 ± 20	79.1 ± 8.6	0.31 ± 0.16	91.2 ± 21.8	Urinary ACR µg/mg 55 (17–376), 11 had normoalbumiuria, 12 micro, 10 macro, 17 were using ACE or ARB and 2 were using diuretics	NS
Hassanein 2017	7.3 ± 0.8	87.1 ± 14.8	129 ± 11.7	78.2 ± 6.7	NS	89.9 ± 19.6	NS	NS
During Ramadan								
Abdelgadir 2019	NS	NS	NS	NS	NS	NS	NS	No. hypoglycemic events during Ramadan (n/Sensor) 3.9 ± 5.1
Bashier 2018	NS	NS	NS	NS	NS	NS	No change	113 patients with hypo, 93 checked BG BG <70 mg/dL
WanSeman 2016	NS	NS	NS	NS	NS	NS	NS	No. events
Shao 2018	NS	Mean ± SEM −1.8 (0.4)	Mean ± SEM −8.1 ± 2.8	Mean ± SEM −3.7 ± 1.3	Mean ± SEM −0.01 ± 0.01	Mean ± SEM −6 ± 1.5	NS	NS
Hassanein 2017	NS	NS	NS	NS	NS	NS	NS	NS
After Ramadan								
Abdelgadir 2019	7.6 ± 1.1	81.9 ± 15.5	135 ± 15.4	71 ± 8.9	NS	99 ± 16.8	0.7 ± 0.2	NS
Bashier 2018	7.8 ± 1.3	83.8 ± 16.6	NS	NS	NS	NS	NS	NS
WanSeman 2016	7.65 ± 0.44	NS	NS	NS	NS	NS	NS	NS
Shao 2018	NS	NS	NS	NS	NS	NS	NS	NS
Hassanein 2017	NS	85.3 ± 14.3	127.9 ± 10.2	75.9 ± 7.3	NS	88.4 ± 21.6	NS	NS

ACR, albumin : creatinine ratio; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BG, blood glucose; BR, before Ramadan; NS, non-significant; OHA, oral hypoglycemic agents; SBP, systolic blood pressure; SEM, standard error of the mean; SGLT-2, sodium–glucose cotransporter 2.
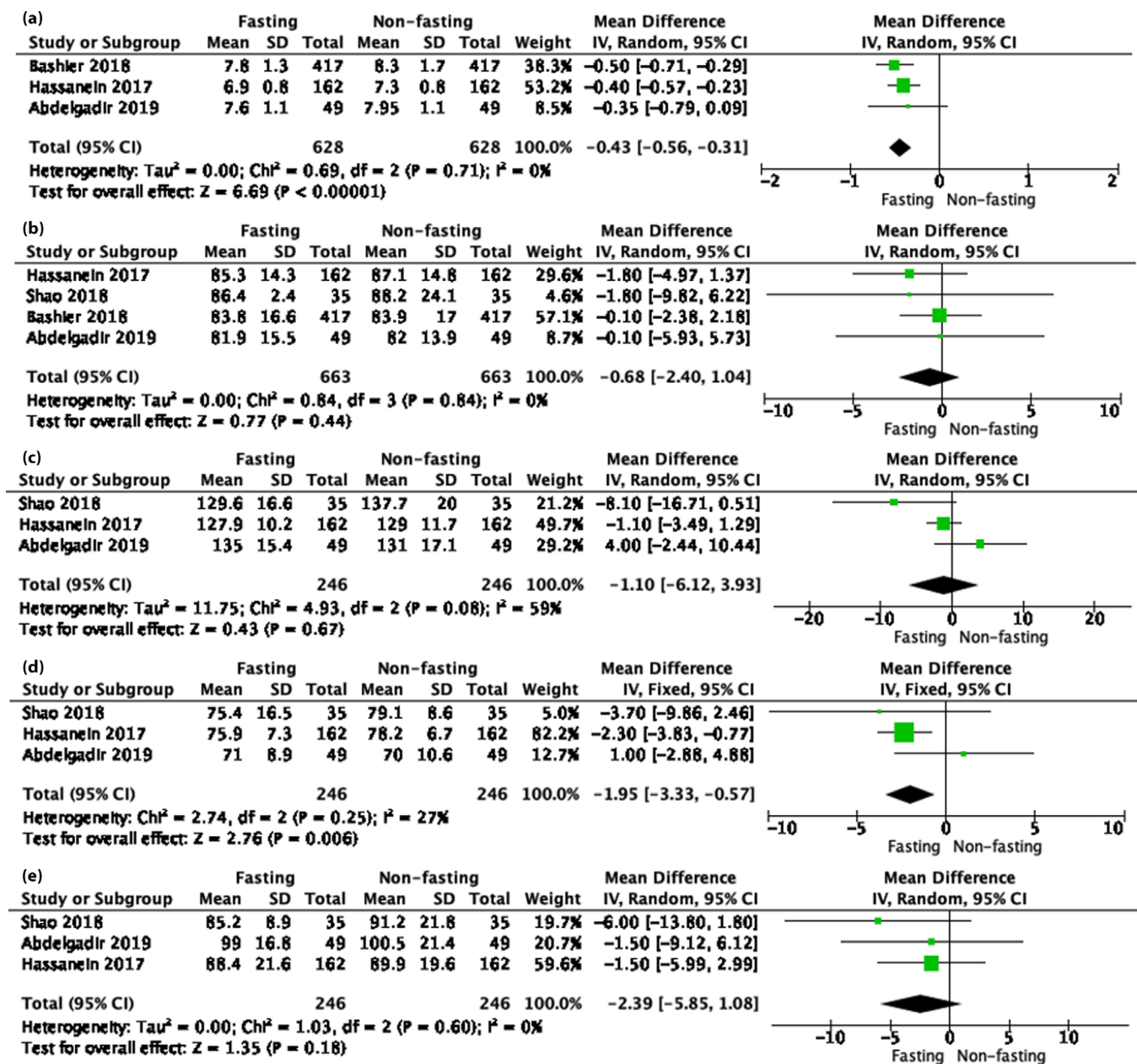
Figure 2 | (a) Forest plots of glycated hemoglobin (%) during/after Ramadan fasting versus pre-Ramadan in patients with type 2 diabetes mellitus. (b) Forest plots of weight (kg) during/after Ramadan fasting versus pre-Ramadan in patients with type 2 diabetes mellitus. (c) Forest plots of systolic blood pressure (mmHg) during/after Ramadan fasting versus pre-Ramadan in patients with type 2 diabetes mellitus. (d) Forest plots of diastolic blood pressure (mmHg) during/after Ramadan fasting versus pre-Ramadan in patients with type 2 diabetes mellitus. (e) Forest plots of estimated glomerular filtration rate (mL/min/1.73 m^2) during/after Ramadan fasting versus pre-Ramadan in patients with type 2 diabetes mellitus. CI, confidence interval; SD, standard deviation.

Hypoglycemic events

Abdelgadir *et al.*[12] reported a lower number (3.9 ± 5.1 vs 5.0 ± 6.9) and duration (62.8 ± 68.5 vs 89.5 ± 80.7 min) of hypoglycemic events compared with before Ramadan. Bashier *et al.*[13] reported that 27% of 417 patients taking SGLT-2i experienced hypoglycemic symptoms during Ramadan, of which 83.8% were confirmed by a blood glucose reading of <70 mg/

dL and led to 38 patients breaking their fast. The majority (67 episodes, 64.4%) of hypoglycemic symptoms occurred before starting the fast at Iftar[13]. Wan Seman *et al.*[16] reported a significant reduction in symptomatic hypoglycemia from 24.1% before Ramadan to 3.4% in the last week of Ramadan (*P* = 0.004). Documented hypoglycemic events were less common in the group treated with dapagliflozin (7.3%) compared

with sulfonylurea (27%) and none of the patients experienced severe hypoglycemia requiring hospitalization[16]. Hassanein et al.[14] reported two of six (33.3%) hypoglycemic events with a blood glucose <3.9 mmol/L in the SGLT-2i group compared with 27 of 37 (72.9%) in the sulfonylurea group.

Ketonemia and acidosis

Shao et al.[15] reported a minor reduction in β-hydroxybutyrate (from 0.31 to 0.30 mmol/L), with an increase in bicarbonate (0.52 ± 1.66 mmol/L), urea (0.20 ± 1.24 mmol/L) and anion gap (0.79 ± 5.74) in patients treated with SGLT-2i during Ramadan.

Volume depletion and electrolyte imbalance

Hyperkalemia (K^+ >5.5 mmol/L) was reported in four (12.1%) patients on SGLT-2i, but did not differ significantly from controls (3; 10.3%, $P = 0.825$)[15]. There was no difference in the fall in sitting BP between patients treated with SGLT-2i compared with controls ($P = 0.978$), and there was no incidence of postural hypotension[15]. Hassanein et al.[14] reported 51 events of volume depletion (86.3% dehydration, 2% hypotension, 6% postural dizziness) in patients treated with canagliflozin.

Other adverse events

Bashier et al.[13] reported that 39 (9.3%) patients complained of extreme and unusual thirst. Wan Seman et al.[16] reported that 13.8% had symptoms of postural hypotension, 10.3% had urinary tract infection, 3.5% had polyuria, 3.5% had thirst, 1.7% had body itching, 1.7% had skin dryness, 1.7% had nausea and 1.7% had lethargy, but this did not differ from patients taking sulfonylurea. Abdelgadir et al.[12] and Bashier et al.[13] reported no DKA events during Ramadan fasting. Bashier et al.[13] observed no thrombotic events during Ramadan fasting. Hassanein et al.[14] reported that 10 of 162 (6.2%) patients taking canagliflozin experienced thirst, one had a urinary tract infection, but there were no genital mycotic infections.

Risk of bias of the included studies

In studies assessing the safety and efficacy of the SGLT-2i during Ramadan, Egger's test resulted in a value of $P < 0.05$ for HbA1c and DBP, showing no significant influence of small study effects (publication bias) on the results. To further assess for small study effect, heterogeneity and potential bias was assessed using the risk of bias assessment ROBINS-I tool for observational studies and the Cochrane Collaboration's tool for randomized controlled studies[19] (Table 2).

Sensitivity analysis

In the event of small study effects, sensitivity analysis was carried out to examine how the results of the meta-analysis change under different assumptions. Due to the inherent difficulty in adjusting for publication bias for the sake of adjustment for heterogeneity and small study effects, we used comparison of

Table 2 | Risk of bias assessment for non-randomized studies

Studies	A	B	C	D	E	F	G
Abdelgadir 2019[2]	●	●	●	●	●	●	●
Bashier 2018[3]	?	?	●	●	?	●	●
Hassanein 2017[4]	●	●	●	●	●	●	●
Shao 2018[5]	●	●	●	●	●	●	●
Wan Seman 2016[6]	●	●	●	●	●	●	●

Yes = ●; No = ●; Unclear = ?. Risk of bias legend: (A) Bias due to confounding. (B) Bias in selection of participants. (C) Bias of classification of intervention. (D) Bias due to deviations from intended intervention. (E) Bias due to missing data. (F) Bias in measurement of outcome. (G) Bias in selection of the reported results.

fixed and random effects models (10.4.4.1), and the trim and fill strategy (10.4.4.2), as per the Cochrane recommendations[19].

Comparing fixed and random effects estimates

Random effects meta-analysis was used for all study variables in anticipation of heterogeneity due to differences in study design and population. However, for those variables that presented a significant publication bias (Egger's test $P < 0.05$), we applied the random effects model to account for the presence of small study effects. Heterogeneity remained the same for HbA1c, weight, systolic BP and eGFR. However, when comparing the random with fixed effects model for DBP, whereas I^2 remained the same, the overall effect size changed from $P = 0.12$ to $P < 0.006$, thus a forest plot was presented in a fixed effects model for this variable. All studies were included to calculate the overall effect size for the meta-analysis.

Trim and fill strategy

When removing small studies to correct for funnel plot asymmetry arising from publication bias (Egger's test $P < 0.05$), the P-value for Egger's test remained the same for HbA1c, weight, systolic BP, DBP and eGFR. All studies were included to calculate the overall effect size for the meta-analysis.

DISCUSSION

Fasting during Ramadan for patients with diabetes carries both benefits and risks related to their medication[20]. As such, current recommendations advocate that patients with diabetes who wish to fast should discuss the risks and benefits of fasting with their healthcare providers, and make adjustments to the dose, timing and type of medication during Ramadan. Several recent systematic reviews and meta-analyses have shown that the newer glucose-lowering therapies have a lower risk of hypoglycemia during Ramadan[21]. The present meta-analysis showed that Ramadan fasting is associated with a ~0.4% decrease in HbA1c in patients treated with SGLT-2i, which is comparable to the reduction observed with dipeptidyl peptidase-4 inhibitors and glucagon-like peptide 1 receptor agonists during Ramadan fasting[21], and the incidence of hypoglycemia was lower

compared with sulfonylureas. Fasting was also associated with minor weight loss in type 2 diabetes mellitus patients taking SGLT-2i, in contrast to the results of a recent meta-analysis showing weight gain during Ramadan[22]. There was no change in systolic BP, but a reduction in diastolic BP in patients taking SGLT-2i. Reassuringly, there was no effect on kidney function, as measured by eGFR, and no evidence of volume depletion, even though all the studies were undertaken in patients who were fasting during the summer months in the Middle East and South Asia.

Treatment with SGLT-2i is associated with mycotic infections, especially in the elderly[23]. The present meta-analysis shows no increase in the incidence of mycotic infections in patients treated with SGLT-2i during Ramadan. SGLT-2i-induced DKA was not observed in any of the included studies, and there was only one reported event of increased anion gap with a low risk of dehydration and ketoacidosis. However, ketone bodies were only measured in one study, and the incidence of clinical ketoacidosis during Ramadan in patients with type 2 diabetes is too low to adequately identify an association with the use of SGLT-2i. Nevertheless, acute illness while fasting during Ramadan can lead to metabolic decompensation, due to increased endogenous steroids and catecholamines, and especially with the omission of insulin or other diabetic medications[24]. This argues strongly for all patients who become unwell while fasting to be educated on 'sick-day rules' ensuring adequate blood glucose testing and change in treatment or to cease fasting.

This is the first comprehensive meta-analysis addressing the effect of Ramadan fasting on type 2 diabetes mellitus patients treated with SGLT-2i. However, there is considerable heterogeneity among the included studies in relation to their design, other concomitant antidiabetic treatments and duration of fasting among study participants. The limitation of the present meta-analysis was the small number of observational studies included in the analysis and the lack of reporting on the risk factors in the original articles. Head-to-head studies are required with structured outcome reporting on serum creatinine, electrolyte imbalance, hypoglycemia and incidence of ketoacidosis to fully assess the risks and benefits of SGLT-2i during Ramadan.

The present systematic review and meta-analysis shows that SGLT-2i in patients with type 2 diabetes mellitus during Ramadan confer benefits by reducing HbA1c, weight and BP, while lowering the risk of hypoglycemia; without increasing the risk of mycotic infection and DKA in patients with type 2 diabetes mellitus treated with SGLT-2i. Healthcare providers need to continue to individualize treatment plans during Ramadan due to the variable quality of included studies. Furthermore, the present findings urge the need for large randomized head-to-head studies of SGLT-2i against other therapies or placebo during Ramadan.

DISCLOSURE

The authors declare no conflict of interest.
Approval of the research protocol: N/A.
Informed consent: N/A.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Search strategy
Appendix S1 | PRISMA 2020 checklist.