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REVIEW

Effects of Ramadan Fasting on Glycaemic Control Among Patients with Type 2 Diabetes: Systematic Review and Meta-analysis of Observational Studies

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ABSTRACT

Introduction: The prevalence of type 2 diabetes (T2D) is increasing around the world. Although Muslims with a physical illness are exempted from fasting during the month of Ramadan, a great number still choose to fast, often without medical consultations. The aim of this systematic review and meta-analysis was to investigate the impact of observing Ramadan fasting (RF) on glycaemic control in patients with T2D.

Methods: The Web of Science, Scopus, EBSCOhost, CINAHL, ScienceDirect, Cochrane Library, ProQuest Central and Europe PubMed Central (Medline) databases were searched for relevant studies published between January 2000 and December 2021. Observational studies that examined the changes in body weight (BW) and glucose parameters (glycosylated haemoglobin [HbA1c] and fasting blood glucose [FBG]), before and after RF among different age groups with T2D were included in the systemic review and meta-analysis. Effect sizes for the tested outcomes were calculated as weighted mean difference (WMD), with their confidence intervals (CI). Quality assessment was examined using the National Heart, Lung, and Blood Institute (NHLBI) tool.

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Results: Of the 1592 identified records, 12 studies conducted in Middle Eastern and Asian countries were eligible and included in the quantitative analyses. The quality of the retrieved studies was evaluated and found to range between fair (83%) and good (17%). These 12 studies included 5554 participants of whom 54% were males and 46% were females. Our pooled analysis demonstrated that HbA1c and FBG levels significantly decreased after RF when compared to the pre-fasting levels (WMD = 0.55 mg/dl, 95% CI 0.33–0.77, $P < 0.00001$, $I^2 = 93\%$ and WMD = 12.42, CI 6.46–18.38, $P < 0.0001$, $I^2 = 81\%$, respectively). However, the difference in BW in fasting patients after RF versus the pre-fasting stage was non-significant. Although, young patients with T2D were enrolled in the 12 selected studies, we did not find any studies that solely focussed on this group.

Conclusion: The impact of RF on adult patients with T2D is associated with favorable outcomes. However, future studies should evaluate data from young adults separately. In addition, it is essential to identify the effects of the number of fasting days (level of exposure), diet, level of physical activity and sleeping pattern on optimal glycaemic control. This information could be utilized by medical professionals as a non-pharmacological therapeutic method for management of diabetes in patients who are willing to practice fasting during Ramadan and other months of the year.

Study Registration: PROSPERO: CRD42022314752.

Keywords: Intermittent fasting; Type 2 diabetes; Early onset diabetes; Glycaemic control

Key Summary Points

Type 2 diabetes (T2D) has increased dramatically in recent decades, and early-onset disease has an aggressive nature.

A considerable proportion of patients with T2D observe Ramadan fasting (RF) each year, and the impacts of RF on young adults with T2D are not well known.

The results of this meta-analysis revealed that RF has the potential to improve glycaemic control parameters among patients with T2D.

The comprehensive systematic review revealed that no study recorded in the databases that were searched investigated the impact of RF specifically in young patients with T2D.

The meta-analysis revealed that all of the available studies that included young patients did not provide a precise description of the data for different age groups and that the data presented was based on the mean or median of the investigated age groups.

INTRODUCTION

Around 24% of the world population observe Ramadan fasting (RF) for 1 month (29–30 consecutive days) every year. In this kind of intermittent fasting, Muslims abstain from food and drinks for 12–20 h per day, from dawn to sunset [1]. Fasting during Ramadan is obligatory for all Muslims from the age of puberty at around 12 years [2, 3]. Several studies have examined the impacts of RF on healthy people and patients with chronic conditions [4, 5]. In some cases the findings are contradictory, possibly due to wide variations in study designs and methods used to measure and assess the metabolic parameters [6]. It has been reported that RF is safe and that it significantly impacts body weight (BW) reduction among adult patients with type 2 diabetes (T2D) [7–10]. More than 95% of patients with T2D (including adults and young adults aged > 18 years) reported that their lifestyle changes significantly during the month of Ramadan [11], including changes in meal patterns (food and fluid intake), sleeping patterns (duration and quality) and physical activity [12, 13]. These changes could have a subsequent impact on blood glucose control among patients with early-onset and adult-onset T2D. In one study, about 60% (n = 92) of patients with T2D reported reducing their insulin dose during Ramadan and around 8% reported stopping taking insulin entirely [14]. The authors of this study also reported that all patients who had dose adjustments during Ramadan had a significant reduction in glycosylated haemoglobin (HbA1c).

The impact of RF on patients with T2D has been extensively studied in recent decades. In 2017, an international and annually updated comprehensive practical guide for patients with diabetes was developed to be used by medical professionals during the month of Ramadan [15]. However, the effects of RF on different age groups, including young people with T2D, have not been investigated concretely. The World Health Organization defines young people as being between the ages of 10 and 24 years [16]. Some studies have included this age group as a part of the targeted population, but the data were presented as either mixed with the data on adult patients or with the data on other patients with other kinds of diabetes, such as type 1 diabetes (T1D). Moreover, the impacts of age and the time of onset of T2D must be taken into consideration in all relevant research as these data will prevent any reporting bias, and the findings would be valid and can be used in evidence-based practice. Therefore, reviewing and synthesizing the effects of RF by comparing patients with T2D of different age groups is important: first, to identify, via comprehensive systematic research, whether these effects have has been properly studied before or not; second, to provide valuable evidence on whether RF observed by patients with T2D is beneficial or associated with significant harm. Subsequently, this information will help identify the quality of the current research and explore the similarity/variations between different age groups. Importantly, the best approach/recommendation that could be applied in future studies can be then developed. In addition, the synthesized data could assist healthcare professionals to create new approaches and tailor new guidelines that help to provide optimal care for those patients during Ramadan.

The aim of our systematic review and meta-analysis was to examine the impacts of observing RF on patients with T2D, among different age groups. This has been evaluated by comparing each patient's glycaemic control biomarkers (HbA1c and fasting blood glucose [FBG]) and BW before and after the month of Ramadan. Therefore, we first critically appraised all relevant literature published in the last 20 years and then carried out a meta-analysis to address the following questions: (1) What are the effect sizes for the impacts of RF on FBG levels and HbA1c in patients diagnosed with T2D? (2) How could these patients' BW be influenced by fasting during the month of Ramadan?

METHODS

This review was reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement, explanation, and elaboration [17, 18]. The study protocol was developed and published in PROSPERO on 21 March 2022 under ID number CRD42022314752.

Population and Study Design

This review included studies which evaluated Muslims of different age groups who had been diagnosed earlier with T2D and who decided to fast during the month of Ramadan. Only studies that investigated young adult patients (12–24 years old) with T2D as a part of the study population were included; studies that did not include young people with T2D were excluded. Patients with T2D and comorbidities, such as chronic illness and/or obesity, were also included in the analyses. Studies that were restricted only to healthy people, pregnant women, athletic people and patients with T1D were excluded. This review included all observational quantitative studies, including prospective, retrospective, cross-sectional and pilot studies. Interventional studies, such as randomized controlled trial studies, were excluded, as were all other types of clinical trials, qualitative studies, commentaries, letters and editorials. Similarly, studies that did not report or measure the outcomes levels were excluded. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Exposure

Fasting during the month of Ramadan was considered to be the main exposure, and all other studies which included other specific interventions (such as intensive educational programmes and introduction of new medications) were excluded. This study was designed to minimize the number of confounding factors and focus solely on fasting per se. However, if patients were just asked to reverse their medications at sunset and dawn, and the education programme was considered to be part of the patient's standard medical care, these situations were not considered to be a specific intervention. Studies were included only if there are at least two data points, before and after or at the end of the month of Ramadan.

Comparators and Outcomes

The comparator was pre-fasting versus post-fasting. Therefore, HbA1c and FBG were considered to be the primary outcomes examined before and after or at the end of RF; random blood sugar (RBG) and BW were considered to be secondary outcomes. Conference papers and unpublished data were included. Google Translate was used to translate some articles. Outcomes should be presented in measurable units expressed in numerical form. Data presented in terms of figures, graphs or curves were excluded unless obtained from the authors. The corresponding original author(s) was (were) contacted via emails and ResearchGate messages to request the primary data for some outcomes. This review included all recently published studies worldwide throughout the period from 2000 to 2021. The two data points were defined as follows: (1) outcomes collected before fasting were all data collected in the month immediately preceding the month of Ramadan and up to the first few days of Ramadan; (2) outcomes collected after fasting were all data collected at the end of Ramadan and up to 1 month after the cessation of the month of Ramadan.

Information Sources and Search Strategy

Two reviewers (HE, DA) independently searched nine electronic databases: Web of Science, Scopus, EBSCOhost, CINAHL, ScienceDirect, Cochrane Library, ProQuest Central, thesis databases (British library EThOS, DART-Europe) and Europe PubMed Central (Medline). All databases were searched during the period from January 2000 to December 2021. The search period was so specified to include the most recent peer-reviewed studies. To avoid missing any important articles, the snowball technique was followed by scanning the reference lists of a number of important studies, such as narrative reviews, other systematic reviews and meta-analyses related to RF and T2D. The review team members manually searched other sources, such as the Gray literature (Google Scholar, dissertations, Open Gray) and some popular journals in Ramadan, such as the *Journal of Muslim Minority Affairs*. Moreover, to identify further studies, one of the most important authors, in RF research, Mohamed Hassanein was contacted with a request for unpublished and published data.

Medical subject heading (MeSH) and the most common keywords pertaining to RF were used to develop the search strategies to identify the relevant literature (Table 1). To identify as many studies as possible, the restriction in the research setting was only applied to the published years, as stated above. Google Translate was used to translate some reports which were

Table 1 Search strategy techniques followed in all databases

Population/patients (participants)	AND	Exposure	AND	Comparisons or outcomes	AND	Study design
Type 2 diabetes		Ramadan fasting		Weight/obesity		Observational
OR		*OR*		*OR*		*OR*
T2D		Islamic fasting		Blood glucose (MeSH)		Retrospective
OR		*OR*		*OR*		*OR*
Diabetes		Ramadan Intermittent fasting		Glucose		Prospective
OR		*OR*		*OR*		*OR*
Diabetes Mellitus, Type 2 (MeSH)		Intermittent fasting		Metabolites		Questionnaire-based studies
OR		*OR*		*OR*		*OR*
Diabetes mellitus (MeSH)		Ramadan diurnal intermittent fasting		Biological changes		Non-interventional
OR		*OR*		*OR*		*OR*
Insulin resistance		Caloric restriction		Blood biomarkers		Case–control studies
OR		*OR*		*OR*		*OR*
Non-insulin-dependent diabetes		Recurrent Circadian fasting		Glucose homeostasis		Cohort studies
OR		*OR*		*OR*		*OR*
Adult-onset diabetes		Ramadan model of intermittent fasting		HbA1c		Follow-up studies
OR		*OR*		*OR*		*OR*
Young adults with diabetes		Intermittent prolonged fasting during Ramadan		Glucose parameters		Longitudinal studies
OR		*OR*		*OR*		*OR*
Adolescents with T2D OR Diabetes		Fasting (MeSH)		Carbohydrate metabolism (MeSH)		Cross-sectional studies
OR		*OR*		*OR*		*OR*
Adults with diabetes		Muslim fasting		FBG		Cross-over studies
OR		*OR*		*OR*		

Table 1 continued

Population/patients (participants)	AND	Exposure	AND	Comparisons or outcomes	AND	Study design
Early-onset diabetes		Ramadan n3 fasting		RBG		

FBG Fasting blood glucose, *HbA1c* glycosylated haemoglobin, *MeSH* Medical subject heading, *RBG* random blood glucose, *T2D* type 2 diabetes

in languages other than English. A Health Sciences Librarian from De Montfort University was consulted on how to create the best research strategies. A search terms table was developed based on the PICO (Patient/Problem, Intervention, Comparison and Outcome) strategy and using several searching tools (truncation symbol*, phrase searching [adjacency/nearness], Boolean logic [OR, AND, NOT]) (Table 1). Subsequently, an EBSCOhost search strategy was developed by one of the authors (HE) and adapted to the other databases and search syntax, after being discussed thoroughly with all other co-authors (search history from several databases is provided in the Electronic Supplementary Material [ESM] file S1).

Selection Process

The records were screened by two authors (HE, DA) independently of each other. The results were then combined and reassessed according to the inclusion and exclusion criteria. Any disagreement on a selected study was resolved by discussion until a consensus was reached. Literature results from all databases were exported to the reference manager software, RefWorks, which was used to manage references and share the collected data among the review team. However, some authors preferred to use Microsoft Excel spreadsheet (Microsoft Corp., Redmond, WA, USA) for screening. First, the title and the abstract were screened using different approaches. RefWorks has some tools that were used to automatically eliminate less relevant records using priority screening. In addition, the duplicates were removed from all records before the start of the screening process. All eliminated records are reported in the PRISMA flow chart (Fig. 1). At the same time, all texts of the interesting records were retrieved and the unretrieved data were collected in a separate folder.

We requested the full text of the publication from a number of corresponding authors via ResearchGate. The full texts were screened for eligibility, and the corresponding authors were contacted again when needed. However, not all of the corresponding authors responded to the reviewers' queries. The reasons for the excluded records are illustrated in the PRISMA flowchart (Fig. 1). Some texts were translated via Google Translate to confirm eligibility. A translation provided by a native speaker (Arabic language) was also used.

Data Collection Process

Data collection was carried out by one author (HE) twice and verified by the other co-author (AA) to reduce the risk of error and bias. To obtain missing and unclear data, we contacted the corresponding author(s) of the original article via email, ResearchGate or social media (such as Twitter and WhatsApp, when available). However, of the six corresponding author(s) contacted, only two responded and provided the requested data. Data were extracted manually from all studies, and no specific automatic tools were used. Once extracted, the data of the investigated outcomes were organized in a way that could be easily entered into Review Manager (RevMan) software, which was used later for the meta-analysis. All measured units of outcomes were homogenized. Data extraction was divided into two files: (1) the first

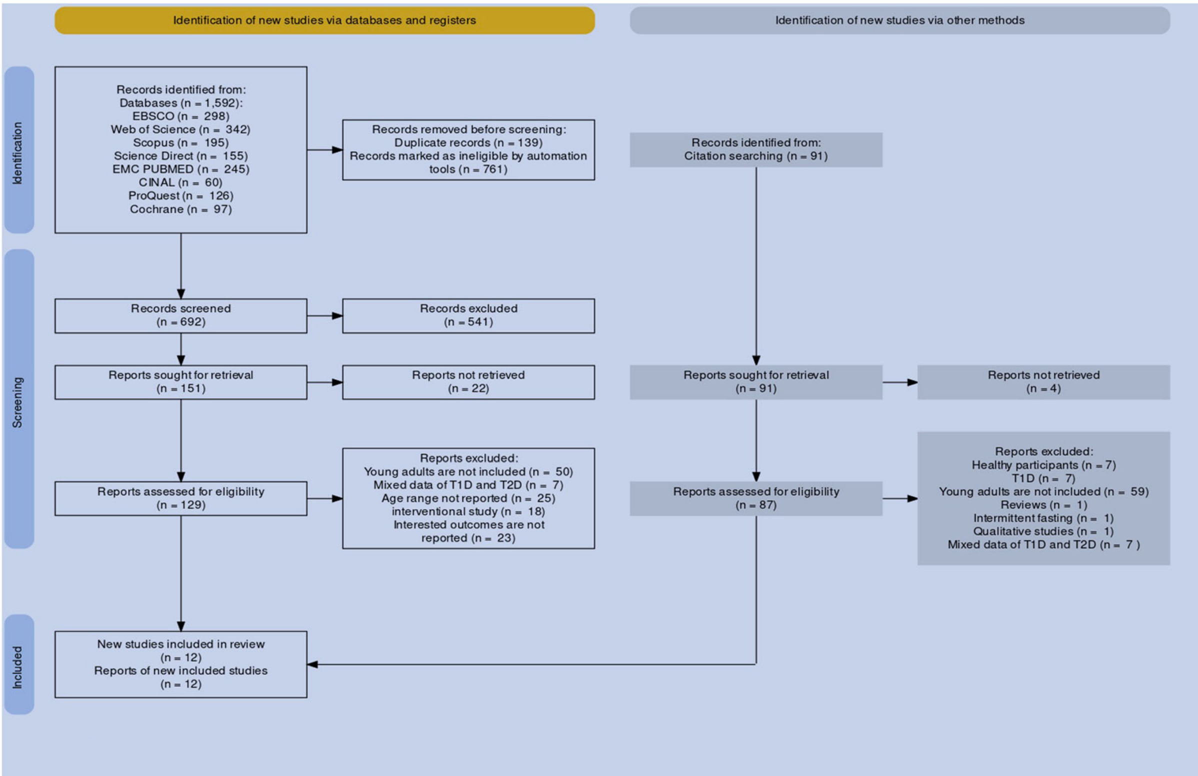

Fig. 1 PRISMA flow diagram of study selection process

file included the study's characteristics, as demonstrated in Table 2; (2) the second file included the numeric outcomes of all the included studies before and after the month of Ramadan (ESM file S2).

Data Items

According to the inclusion criteria, this review targeted the summarizing of all the studies that included the young age groups (12–24 years). However, in the original studies, outcomes based on age groups were not studied; therefore, we assumed that the analysed results reflected all of the included age groups equally. We attempted to obtain the primary data for each study, but this was not possible. In addition, some of the collected data items which were not clearly reported were estimated based on the year of the study, such as the season/temperature and the average number of fasting hours. Regarding the measuring points of the outcomes, outcomes measured within the period from 3 to 6 months, assumed to be the nearest results, could reflect the reading before and after RF. This was taken as an assumption of the eligibility criteria of the review.

Data extracted from the selected studies were: authors' names and the year of publication; location and season of the study; patients' characteristics (duration of the disease, medication taken, gender, average and age range); sample size; exposure (fasting days during the month of Ramadan); time of data collection before Ramadan; time of data collection after the month of Ramadan; and outcomes and effect measures (BW, HbA1c, FBG, RBG). All of these outcomes are continuous numeric variables, and mean differences in measures were used to analyse the difference between the two points measurements: before and after fasting the month of Ramadan.

Primary outcomes were HbA1c and FBG. These parameters were chosen because they are the most commonly examined parameters

Table 2 Characteristics of the 12 studies ultimately included in the meta-analysis

Author name, year of publication	Country (city)	Age range and mean ± SD (yr)	Total Population (n), age group (n)	Male/female n (%)	Duration of diabetes means (SD)	Types of medication	Associated comorbidities	Ramadan year	Season	Fasting days	Fasting hours	Time of measurement before Ramadan fasting	Time of measurement after Ramadan fasting
Hassanein et al, 2021 [26]	UAE, Dubai	18-80/Mean age was 54	342	M 52.3% (n = 180), F 47.7% (n = 162).	NR	(OHA) with or without insulin.	NR	NR	NR	NR	NR	Within 3 months	Within 3 months
Patel et al, 2007 [23]	Oman Dhahira region	24-95/ 54.3 ± 11.7	334 <45 (70) 45-55 (85) 55-65 (115) ≥ 65 (64)	F (188) 56.3%, M (146) 43.7%	5.8 ± 5.1	Insulin/ (OHA)	coronary artery disease (19.5%), neuropathy (10.2%), retinopathy (9.3%), nephropathy (6.0%), hypertension (60%)	2006	NR [Estimated to be Autumn [Average temperature was 22°C]	93.1% of the participants fasted for 30 days	NR [estimated to be around 12 hours]	Just before Ramadan	Just after Ramadan
Bener et al, 2014 [21]	Qatar	≥18/ [45.9±15.3]	1301 < 30 (247) 30–39 (169) 40–49 (266) 50–59 (408) ≥ 60 (211)	M 675(51.9%)	NR	Insulin and/or (OHA)	NR	2013	NR	NR [assumed to be the whole month of Ramadan	NR	At the beginning of Ramadan	NR [measurement reflects the fasting for the whole month of Ramadan]
Jehangir et al,2020 [29]	Pakistan	>18/ [44.6+10.15]	103	M 66% (68), F 34% (35)	NR	Insulin and/ OHA	NR [Moderate to high-risk comorbidity	2019	NR [Estimated to be from 11.0°C - 30.7°C]	NR [assumed to be the whole month of Ramadan	NR [estimated to be around 14 hours/day	3 months	One month
Mohamed et al, 2021 [22]	Saudi Arabia (Najran)	>18/ [42.3 ± 12.4]	289 18–30 (116) 31–50 (158) 50 (15)	M 175 (60.6), F 114 (39.4)	162 patients were more than 10 years, and the rest were <10 years	NR	NR/ Patients with serious complications were excluded	NR	Summer [Average temperature was 38.9°C]	NR [assumed to be the whole month of Ramadan]	Approximately 13 hrs	1 month	1 month
Raza et al, 2021 [27]	Pakistan	>18/ [50.9± 10.3]	220 <50 (101) 50–64 (99) >64 (20)	M 129(58.6), F 91(41.4)	3.1 (3.8)	OHA	NR [moderate and high risk]	2019	Not reported [Estimated to be varied from 11.0°C - 30.7°C]	NR [assumed to be the whole month of Ramadan]	NR [estimated to be around 14-15 hours/day	6-8 weeks	4-6 weeks
Alghamdi et al, 2020 [20]	Saudi Arabia (Riyadh)	22-75/ 51 ± 10	82 ≤ 40 (13) 41–50 (24) 51– 60 (27) > 60 (18)	F 54% (n=44), M 46% (n=38)	10.73 ± 8.23	Insulin/ OHA/ with diet and/or exercise	Hypertension Hyperlipidemia	2018	Average temperature 32.4°C to 46.5°C	NR [assumed to be the whole month of Ramadan	15 hours	2 weeks	2 weeks
Hassanein et al, 2017 [25]	Middle East [Lebanon, Kuwait, and the United Arab Emirates [UAE]]	18-65/sulphonylurea group; 54.3 (7.4), canagliflozin group; 52.3 (7.7)	sulphonylurea group; 159, canagliflozin group;162	sulphonylurea group; M 87 (54.7), F 72 (45.3)/ canagliflozin group; M100 (61.7), F 62 (38.3)	sulphonylurea group; 7.6 (5.5), canagliflozin group; 6.5 (5.9)	OHA	NR	2016	Temperatures reached up to 45-50°C in Kuwait and the UAE	The mean (SD) was 29.5 (1.6) canagliflozin and 28.6 (4.1) days with sulphonylurea	15 hours	8 weeks	8 weeks
Hassanein et al, 2019 [11]	Middle East and North Africa (MENA)	≥18/ (55.2± 11.1)	1746	M(973) 55.6%	10.2± 8.0	OHA and/or insulin	Diabetic neuropathy, retinopathy, nephropathy	2016	Summer [Average temperature was 41°C]	27.7 (5.0) days and 57.3% fasted for the full duration of Ramadan.	NR [Estimated to be from 14- 15 hours]	6 months	1-2 months
Siwa et al, 2014 [14]	Singapore	>21 / 56.7 ± 9.1	153	M 57 (37.3), F 96 (62.7)	13.2 ± 9.1	No medication /OHA and/or insulin	Hypertension, hyperlipidemia, and neuropathy [4 ± 2]	2012	NR [Estimated to be around 28°C]	26 ± 5	NR [Estimated to be from 14- 15 hours]	1 month	1 month
Shaikh et al, 2021 [28]	India	≥ 18, 53.0 ± 10.6	246	F 112 (45.5%	5.8 ± 6.6	OHA	Cardiovascular, arterial hypertension, and dyslipidemia	2019	NR [Estimated to be around 29°C-35°C]	NR [assumed to be the whole month of Ramadan	NR [Estimated to be from 14- 15 hours]	6-8 weeks	4-6 weeks
Bashier et al, 2017, UAE [24]	UAE (Dubai)	>18/54.0 ± 11.6	417	F 58.5%	13.4±6.6 years	Insulin and/or OHA	NR	2016	NR [Estimated to be around 41°C]	> 20 days	NR [Estimated to be from 14- 15 hours]	1 month	6 weeks

OHA (oral hypoglycemic agent), NR (non-reported) when evaluating the effects of dietary and pharmacological interventions on patients with diabetes. FBG is crucial in determining whether fasting is safe or not for these patients. HbA1c is important for identifying the impact of fasting on improving the disease condition in general and its potential in reversing the disease. This is particularly paramount in adolescent and young adult patients who are not usually responding to the standard treatment. Consequently, HbA1c data will provide a scientific background to the clinical practice to provide support for all patients who usually observe Ramadan and practice any other kinds of fasting beyond the month of Ramadan. The secondary outcomes were BW and RBG. Analysing these outcomes is valuable in terms of obtaining adequate information on the effects of RF on glycaemic control in patients with T2D. It is well known that people who are overweight/obese could develop complications related to disease progression. However, little information on RBG was available from the included studies, and this outcome was therefore not included in the meta-analysis.

Risk of Bias in Individual Studies

The risk of bias (ROB) in the included observational studies was assessed based on the study quality assessment tool developed by the National Heart, Lung, and Blood Institute (NHLBI) (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). This assessment was performed by two reviewers (HE, AA), and overall judgment was reached via discussion. In this method, 14 questions were answered using YES, NO, NA (not available) and NR (not reported) from each study, and then the results of all the questions were assessed as good, fair, or poor. This is critically discussed in the following text and linked to the final review findings. A Microsoft Excel spreadsheet was created to conduct the quality assessment of all the included studies.

Data and Statistical Synthesis

Since this review was investigating the impact of RF (the main exposure) on those outcomes that reflect glycaemic control in patients with T2D, all of the eligible studies were included in the study synthesis. The unit of measurement of all the outcomes was evaluated to make it homogenous. For example, FBG was converted from millimole per litre (mmole/l) to milligram per decilitre (mg/dl) using the following formula: mg/dl = mmol/l × 18. Also, the median/interquartile range (IQR) was converted to mean/standard deviation (SD). The median was assumed to be the mean and the SD was calculated as IQR/1.35. The meta-analysis was conducted using Review Manager, version 5.4 (Nordic Cochrane Center, Copenhagen, Denmark), and the forest plot figure for each outcome was produced to evaluate the pooling results. The random-effects model was selected to examine the effect size as it is anticipated to see the kind of variations between studies in terms of the sample size and participant's age and the points of the outcome's measurement. As all the outcomes were continuous, the measures of the treatment effect were analysed using the weighted mean difference (WMD) with a 95% confidence interval (CI). This was done by calculating the mean difference between the measured outcomes before and after RF while taking into account the sample size of each study.

The level of heterogeneity among studies using the same software was determined. This was tested via the Higgins I^2 statistic (0–40%: might not be important; 30–60%: may represent moderate heterogeneity; 50–90%: may represent substantial heterogeneity; 75–100%: considerable heterogeneity) [19]. The sensitivity analysis was performed by applying the leave-one-out sensitivity analysis to evaluate the influence of each study on the pooled measures by omitting one single study in each turn and recalculating the overall effect size for the remainder. This procedure allowed the reviewers to assess the robustness of the results and explore the source of heterogeneity. Funnel plots and a visual inspection were used to explore the potential for reporting bias among the studies.

RESULTS

Our search of the chosen databases yielded a total of 1592 articles eligible for inclusion in the systematic review (Fig. 1). As a first step, all duplicates were removed (n = 139), then the automation tools of RefWorks were used to eliminate irrelevant records. The 692 records remaining after these two steps were then screened for the title and the abstract. As a result, 541 articles were excluded, 22 records were not retrieved and 129 were evaluated for full-text eligibility. During the selection process, other studies were excluded for several reasons, such as not including young adults (age range 12–24 years) within the targeted study population (50), studies with mixed data involving T1D and T2D (n = 7), non-reporting of the age range (n = 25), intervention studies (n = 18) and outcomes not reported (n = 23). In addition, a total of 91 studies were identified via citations and all these studies went through the second screening process, as illustrated in Fig. 1. Ultimately, a total of 12 studies with 5554 participants (age range 18–95 years) met the inclusion criteria and were included in data synthesis and meta-analysis.

Characteristics of Studies

Table 2 shows the baseline characteristics of the 12 included studies. Given the predominance of Muslim communities, most of the studies were conducted in Middle Eastern countries [11, 20–26], with the exception of two studies conducted in Pakistan, three studies in South Asia (Pakistan and India) [27–29] and one study in Southeast Asia (Singapore) [14]. The age range of the investigated T2D patients varied widely in and across studies, ranging from 18 to 80 years and from 24 to 95 years in some studies [23, 26]. The classification of age groups also varied between studies, and the proportion of young participants with T2D was around 20–40% in some studies [21, 22, 27]. However, approximately half of the studies did not report age group classifications and represented the data based on the mean of the total population, even though the included age group was ≥ 18 years [11, 14, 24–26, 28].

In most studies, the proportion of male participants was generally slightly higher than that of females. There was a noticeable variation in the duration of diabetes between studies, with a mean variation of 3 to 13 years. The patients of interest were either on oral hypoglycaemic agents (OHA) and insulin or on insulin monotherapy. Patients had several comorbidities, including hypertension, cardiovascular disease and hyperlipidemia and nerve damage; these were not reported in some studies [21, 22, 26, 27]. More than half of the studies did not report the season, and the temperature was estimated based on the Ramadan year, which varied between autumn and summer seasons [14, 21, 23, 24, 26–29].

Four studies were conducted in the summer season and the temperature varied from 32.4°C to 50°C in some cities [11, 20, 22, 25]. The average number of fasting hours varied from 14 to 15 in most of the studies. Patients reported fasting for 20 days up to the whole month of Ramadan (29–30 days). However, fasting for the whole month of Ramadan was not reported precisely in most of the studies. The two points of measurement for the interesting outcomes were done within a few months before and after the month of Ramadan, as summarized in Table 2.

Synthesis of Results

Glycosylated Haemoglobin

Twelve studies reported the impacts of RF on HbA1c (%) in patients with T2D (RF, n = 4667; before fasting, n = 5001) [11, 14, 20–22, 24–29]. The forest plot shows that HbA1c was significantly improved in individuals after RF (WMD = 0.55, CI 0.33–0.77, $P < 0.00001$), compared to before fasting. This was associated with considerable heterogeneity (I^2 = 93%) (Fig. 2).

Fasting Blood Glucose/Fasting Plasma Glucose

Of the 12 selected studies, five studies reported changes in FBG level measured in milligrams per decilitre (RF, n = 3167; before fasting, n =

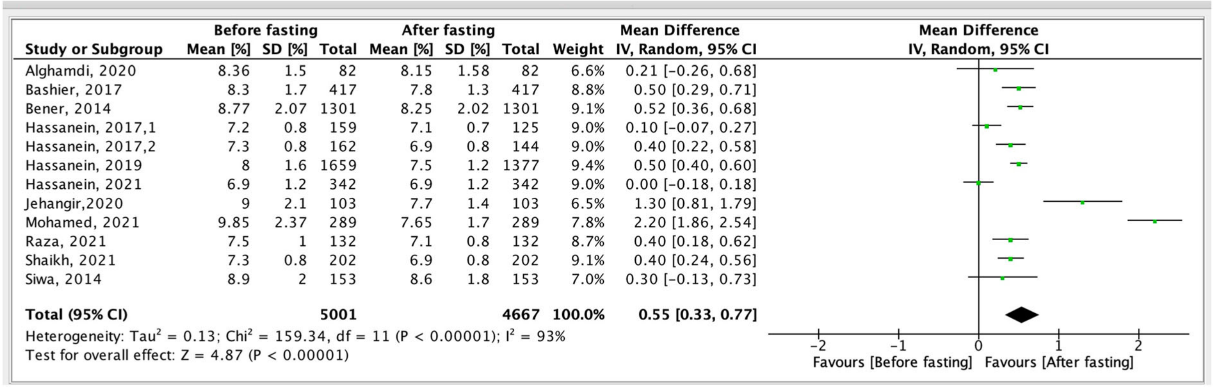

Fig. 2 Forest plot representing the impact of Ramadan fasting on glycosylated haemoglobin (HbA1c) in patients with T2D. See Table 2 for reference citation number. *CI* Confidence interval, *SD* standard deviation

3038 mg/dl) [11, 20, 21, 27, 28]. The pooled analysis showed that RF significantly improved the level of FBG (WMD 12.42, 95% CI 6.46–18.38; $P < 0.0001$), compared to before fasting. The heterogeneity within the studies was considerably high at $I^2 = 81\%$ (Fig. 3).

Body weight

Of the 12 selected studies, 10 studies reported the impact of RF on BW (kg) (RF, n = 3663; before fasting, n = 3769) [11, 20, 23–29]. The pooled data demonstrate that no significant statistical difference was found in BW loss in individuals after 30 days of fasting (WMD 0.64, 95% CI − 0.02 to 1.29, $P = 0.06$), compared to before fasting. The result was not associated with heterogeneity ($I^2 = 0\%$) (Fig. 4).

Risk of Bias of the Included Studies

According to the quality assessment tool used (NHLBI), 10 of the 12 studies were considered to be of fair quality [14, 20–24, 26–29]; the other two studies were considered to be of good quality [11, 25]. Generally, the studies had slightly the same patterns in terms of reporting transparency of the study design and the methods section (ESM file S3). All included studies were designed as observational studies. The aim of the research questions and the study participants were clearly defined in all the studies. Moreover, the eligibility criteria were clearly reported, including similar populations. However, the a description and justification of the sample size were only reported in three studies [11, 20, 25].

Not all studies investigated the difference in the level of exposure (fasting days) with respect to the outcomes of interest. Similarly, three studies reported that the loss of patients during follow-up after the baseline was > 20%. The majority of the studies did not consider moderating factors (age, physical activities and diet) and adjusted their statistical impacts on differences in outcomes before and after RF. The

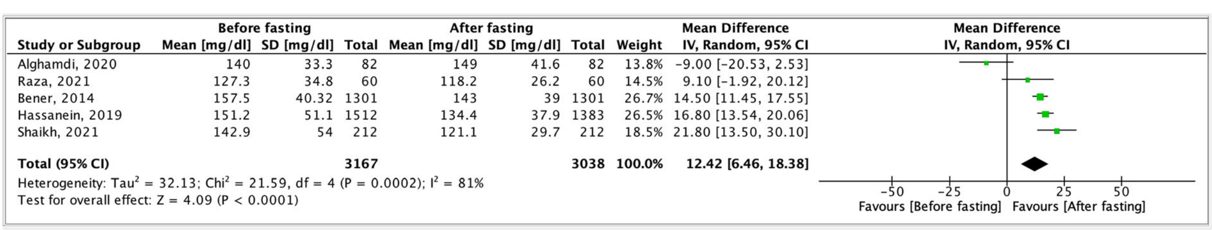

Fig. 3 Forest plot representing the impact of Ramadan fasting on fasting blood glucose levels in patients with T2D. See Table 2 for reference citation number

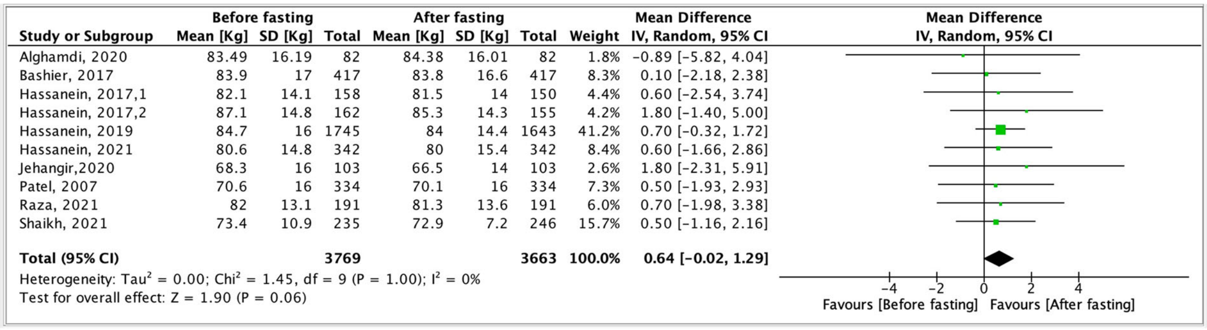

Fig. 4 Forest plot representing the impact of Ramadan fasting on body weight in patients with T2D. See Table 2 for reference citation number

importance of these factors could be highlighted and investigated in future studies of RF and diabetes. More than half of the included studies evaluated the impacts of fasting only once [11, 21–24, 27, 28]. Only five studies investigated exposure more than once over time; in these studies, the outcomes were measured during the fasting period and after the end of fasting [14, 20, 25, 26, 29].

Sensitivity Analysis

To evaluate the contribution of each study to the total effect size and to explore the source of the heterogeneity, we conducted a sensitivity analysis. For FBG, the sensitivity analysis revealed that the main source of heterogeneity was due to the study of Alghamdi et al. [20] and that removing this study from the analysis did significantly change the heterogeneity to a level at which it could be ignored (I^2 = 33%) (effect sizes WMD 15.86, 95% CI 12.90, 18.82; $P < 0.00001$). This was due to the results of this study being in contrast to those of all other included studies (ESM file S4). For the HbA1c, the sensitivity analysis revealed that the main sources of heterogeneity were four studies (of the 12 included studies) that were outliers. Two of these [25, 26] had non-significant results; the other two studies [22, 29] had a smaller effect size compared to the other studies. Removing all four studies from the analysis significantly eliminated the heterogeneity (I^2 = 0), with a slight change in the overall effect size (WMD 0.46, 95% CI 0.40, 0.52; $P < 0.00001$) (ESM file S4). Subgroup analysis was not possible due to the limited data available in the included studies. The produced funnel plots for all of the outcomes showed asymmetric distribution, which traditionally indicates that there is a risk of publication bias (ESM file S5). This risk of publicaton bias was mainly related to the significant impact of the missing small and non-significant studies due to delayed publication and selective reporting. In addition, the asymmetry of the funnel could be affected by the inclusion criteria and the heterogeneity observed between studies.

DISCUSSION

Qualitative studies have reported that a significant proportion of patients with T2D across varying age groups are observing RF each year. All of these patients believe that this tradition is beneficial to their feeling of wellness and provides comfort and happiness while they are socializing with their family members [30, 31]. T2D progresses rapidly and is significantly more varied in younger patients compared to adult patients, in terms of developing comorbidities and consequential psychosocial implications [32]. Thus, highlighting the effects of fasting among these patients is of paramount interest to medical professionals and patients alike. This systematic review found that no previous study has focused specifically on young people with T2D. The results of this meta-analysis were based on the conclusions drawn from observational studies that included both young adults (12–24 years of age) and patients of other age groups. The pooled data showed that the levels of HbA1c and FBG were significantly reduced in people with T2D after the fasting period in comparison with before RF. This difference was associated with considerable heterogeneity. The sensitivity analysis revealed that the reason for the heterogeneity was the inclusion of four outliers and that removal of these four studies from the analysis eliminated the heterogeneity and slightly changed the effect size. This result indicated that there was a form of statistical heterogeneity between studies. However, the RF was not associated with significant weight loss in these patients after the end of the fasting month. This result is supported by a recent meta-analysis that analysed data from observational studies among adults with T2D [33]. The authors of that study reported that fasting during Ramadan had favorable impacts on several metabolic parameters including HbA1c, FBG and lipid parameters, with a slight reduction in BW [33]. Moreover, another meta-analysis [34] analysed data from studies that investigated the effect of Ramadan education programmes on patients with adult T2D. The authors of that study concluded that RF decreased the level of HbA1c in these patients, but they also found that it was associated with weight gain and had no significant effects on hypoglycaemic events [34]. One explanation provided by the authors for these results was that the educational programs were performed via different approaches [34].

Not all of the studies included in this meta-analysis conducted subgroup analysis. Consequently, the data produced reflected the mean age of the study patient population, which was within the middle age group (45–55 years); however, young adults, our target population were also included. Thus, some concerns could be raised regarding our results; i.e. it is not possible to draw a strong precise conclusion on the impacts of RF on young people with T2D. However, the positive effects of RF are optimistic and do confirm the conclusion that fasting during Ramadan can be beneficial. It is urgent that new studies be carried out in the near future. In addition, the considerable heterogeneity in the effect estimates of the investigated outcomes in this meta-analysis is similar to and consistent with outcomes of previous meta-analyses related to RF research [2, 35–38]. These indicate that the variability in the studies included in the present meta-analysis did not occur by chance; it could be classified by Cochrane groups into clinical, methodological and statistical heterogeneity [39]. For example, from Table 2 we see that the study settings of all the studies were different, including geographical location, season and participant's age. Even though the number of fasting hours between studies was quite similar, some relevant data had to be estimated by the reviewers as it was not reported in the studies; consequently, the quality of the study was generally decreased. Likewise, all of the studies were designed as observational studies, and RF was the main exposure; however, the sample size and the sampling time to measure the outcomes varied remarkably.

As a general rule, heterogeneity between studies always exists, and the overall decision of whether to accept or not accept heterogeneity in a meta-analysis is based on the assessment of the author(s). Importantly, the nature of RF studies, which are conducted in different locations with great variations in seasons, fasting hours, and participant ethnicities, provide no other option than to accept a moderate degree of heterogeneity. However, even when these factors are taken into account, people with T2D appear to have a similar biological response to RF. This observation is supported by a previously conducted systematic review, which included observational studies and clinical trials on patients with T2D [40]. The authors of the review noted that RF can be observed safely by these individuals, with no risks of serious complications, and that they can achieve improvements in blood glucose control by adapting their lifestyle and medications before and during fasting. Observational studies have also noted that it is not possible to avoid the significant cultural impacts on the quality and quantity of food/drink intake during the month of Ramadan. For example, it has been reported that people in the Middle East consume a high quantity of carbohydrates, fats, and sugary drinks during the month of Ramadan [41, 42], which would have an impact on the fluctuation of FBG control and BW. The body's physiology is markedly influenced by the change in sleeping patterns during Ramadan [43]. A change in circadian rhythm during fasting has a significant impact on the regulation of various hormones, such as cortisol and insulin, that control the level of blood glucose [12, 44], which could in turn contribute to the large variations in FBG between studies. It could be argued that these alterations could be taken as signs of the response of the body to fasting and that people vary in their response and how long it takes to reach the optimal level.

Another important reason for heterogeneity between studies is the impact of physical activities among patients on the measured outcomes, which has been reported to be considerably reduced during the month of Ramadan [45]. Also, a relationship between glucose control and emotional regulation has been reported in patients with T2D [46]. Patients with diabetes are more sensitive to developing anxiety and depression compared to people without diabetes [47]. Thus, variations in the outcome measures of interest could be influenced, either positively or negatively, by the patient's mental health during fasting. Additionally, the impact of RF on the biological markers is mostly transient, with the levels returning to the pre-RF baseline levels. The authors of one of the studies included in this meta-analysis reported that the patients' weight and HbA1c level were significantly decreased during fasting, but reverted to pre-RF levels within a few months after the end of the fasting month. Therefore, as this meta-analysis aimed to compare the parameters before and after fasting, the pooled data of the BW may relate to the "measurements collected time" after the month of Ramadan, which in turn could explain the non-significant change in BW before fasting versus after fasting. Similarly, a meta-analysis examining the impacts of RF on BW among healthy people showed that the significant weight loss during fasting was transient [48, 49]. This was particularly evident among people who were obese/overweight, with a significant change in healthy-weight participants [48].

In summary, this kind of heterogeneity among RF studies can not be avoided, and the level of moderate heterogeneity should be accepted. Supporting this statement, experts in meta-analysis note that variability in the studies is one of the features of the meta-analysis technique [50]. However, consistency and transparency in reporting RF studies are extremely important. In addition, all moderating factors, such as age, fasting hours, fasting days, and associated comorbidities, must be adjusted for, and the researcher should consider these when interpreting the results. This will help the researcher to draw an accurate conclusion on the impacts of fasting on patients with T2D. Taken together, the results of this meta-analysis shed the light on the impacts of RF on patients with T2D among young adults. We also explored the fact that subgroup analysis was not performed by many of the studies in the literature. Also, this meta-analysis emphasizes the need to consider the fact that the data of patients with T2D at a younger age need to be treated differently by researchers and to compare these data with data on adult T2D patients.

Limitations

This review has a number of limitations. First, even though this meta-analysis included all of the studies that investigated a wide age range of people with T2D, it only reflects the impacts of fasting among adult patients. In addition, subgroup analysis and comparison were not conducted in the majority of the studies. The moderating factor of age was not taken into consideration in analysing the interesting outcomes, and the results reflect only the mean age of the participants included in each study. Most of the studies considered people who were $\geq$ 18 years of age as adult patients with T2D; however, it is well known that disease onset of T2D at around this age progresses differently than adult-onset of T2D (at $>$ 45 years of age). Thus, the data of young patients with T2D should be investigated separately, then compared with data on other age groups, such as the middle-aged and elderly patient populations.

Second, as can be seen in Table 2, missed information from some studies decreased the final quality assessment of each study, which in turn has an impact on the accuracy of the results of this meta-analysis. Many studies were excluded because they mixed data analysis from patients with T1D and T2D, which could affect the obtained results. Thus, accurate recording of patient-related information and the outcome measurements is essential for future research. Moreover, it is well known that randomized trials are the ideal approach in evidence-based research; however, the nature of RF is different, and it is considered as an exposure not as an intervention. Further, most of the studies available in the literature are observational studies, and the number of randomized trials carried out during Ramadan is very limited. Another point to mention, although the type of medications and comorbidities were summarized as part of each study's characteristics, these factors were ignored during the synthesis of the studies as the focus was on exploring the impacts of fasting on young people with T2D. Thus, this meta-analysis cannot draw an accurate conclusion on the impacts of fasting among young adults.

Future Recommendation

There is an urgent need for multi-centre and international studies to investigate the impacts of RF among patients with T2D in the younger age group, particularly in people aged from 12 to 24 years or < 30 years. In addition, when presenting the data from subgroup analyses, it is essential to differentiate between genders and age groups in order to arrive at precise conclusions on and the implications of fasting among these patients. Developing a checklist of guidelines for reporting RF and T2D research/studies is essential. This checklist could be similar to the PRISMA statement/checklists. Such a checklist will enable the researcher to produce high-quality evidence-based research that could be included in meta-analysis and applied ultimately in clinical practice and could be generated by Ramadan research societies such as the Diabetes and Ramadan Alliance (DAR). Investigating the exposure (fasting) more than once is recommended. In addition, identifying the sampling time (before, during and after Ramadan) and the fasting days is extremely important for the results of the study to be reported clearly. Following patients for a longer period after the end of fasting is also recommended for future studies, as this will explore the best approach to maintain the beneficial impacts of fasting.

CONCLUSION

This meta-analysis found that fasting during the month of Ramadan was significantly associated with improvement in glycaemic control parameters in adult patients with T2D. Due to the nature of the month of Ramadan in terms of geographical location, culture, sleeping patterns and number of fasting hours, it was not possible to avoid a moderate degree of heterogeneity. However, the statistical heterogeneity (the variability in investigating the effect of exposure between studies) should be taken into consideration and judicious interpretations of the data are required. This could be minimized by improving the quality of RF study designs and reporting transparency.

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quality of individual studies was assessed by Hala Elmajnoun and Abu-Bakr Abu-Median; any disagreements were discussed with the other co-authors. Data extraction was done twice by Hala Elmajnoun. Hala Elmajnoun was responsible for conducting the meta-analyses and interpretations.

Prior Presentation. This manuscript is based on studies that have been previously presented/ published from different databases, and all provided in the references list.

Disclosures. Hala K Elmajnoun, MoezAlIslam E Faris, Dana N Abdelrahim, Parvez I Haris and Abu-Bakr Abu-Median have nothing to disclose.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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