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Effect of Ramadan fasting on glycaemic parameters & body mass index in type II diabetic patients: A meta-analysis

Neriman Aydın[1], Seval Kul[2], Gülendam Karadağ[4], Suzan Tabur[3] & Mustafa Araz[3]

Departments of [1]Public Health & [2]Biostatistics, Faculty of Medicine, [3]Department of Internal Medicine, Division of Endocrinology, Faculty of Medicine, Gaziantep University, Gaziantep & [4]Department of Public Health-Nursing School, Dokuz Eylül University, İzmir, Turkey

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***Background & objectives*: There has been an ongoing debate about the impact of Ramadan fasting (RF) on the health of these individuals who fast during Ramadan. The aim of this meta-analysis was to evaluate the relationship between RF and glycaemic parameters in type 2 diabetes mellitus (T2DM) patients.**

***Methods*: Search terms were decided and databases such as MEDLINE EBSCO, Google Scholar and EMBASE were searched for eligible studies. Standardized mean differences and 95 per cent confidence intervals (CIs) of post-prandial plasma glucose (PPG), fasting plasma glucose (FPG), glycated haemoglobin (HbA_{1c}) (%) and fructosamine levels were calculated for different treatment regimens.**

***Results*: Of the 40 studies, 19 were found eligible for inclusion in the meta-analysis. Based on pooled results, significant reductions in FPG were found in single oral antidiabetics (OAD) [standardized weighted mean difference (SMD)=0.47, 95% CI=(0.20-0.74)], multi-OAD [SMD=0.36, 95% CI=(0.11-0.61)] and multitreatment subgroups [SMD=0.65, 95% CI=(0.03-1.27)] and overall [SMD=0.48, 95% CI=(0.27-0.70)]. Furthermore, HbA_{1c} (%) [SMD=0.26, 95% CI=(0.03-0.49)] and body mass index (BMI) [SMD=0.18, 95% CI=(0.04-0.31)] were significantly decreased in the multi-OAD group.**

***Interpretation & conclusions*: The meta-analysis showed that RF was not associated with any significant negative effects on PPG and fructosamine levels. However, BMI and FPG and HbA_{1c} (%) were positively affected by RF.**

Key words Fasting plasma glucose - glycated haemoglobin (%) - post-prandial plasma glucose - Ramadan fasting - T2DM

Type 2 diabetes mellitus (T2DM) is the most common type of DM and affects around 95 per cent of people with DM around the world[1,2]. The World Health Organization (WHO) estimated that in 2015, more than 415 million people worldwide were living with diabetes[3], and in 2014, the International Diabetes Federation estimated that diabetes resulted in five million deaths[4].

It is estimated that around 40 to 50 million individuals with diabetes worldwide fast during Ramadan[5]. During fasting, they abstain from eating, drinking, taking oral medications and smoking from sunrise to sunset. Because people fast from dawn to sunset, they consume substantial quantities of sugary foods and carbohydrate-rich meals during non-fasting hours[5]. It is assumed that these traditionally rich

foods associated with Ramadan may present a risk of hyperglycaemia and weight gain for diabetic patients[5]. In healthy people, this fasting does not have any harmful consequences on health[6]. However, it can induce several complications in patients with diabetes[7,8]. There is only one previously published meta-analysis that showed the impact of fasting on health parameters in a healthy population[6]. An outcome of interest of other three meta-analysis was the occurrence of hypoglycaemic events in T2DM patients who fast during Ramadan[9-11]. There is perhaps no meta-analysis that included before-after studies to show any effect of RF on glycaemic parameters used for monitoring T2DM patients. For this reason, this meta-analysis was conducted including all recent studies on T2DM with the aim to demonstrate the impact of RF on the most widely reported health outcomes including post-prandial plasma glucose (PPG), fasting plasma glucose (FPG), glycated haemoglobin (HbA_{1c}) (%), fructosamine levels and body mass index (BMI).

Material & Methods

Literature search: A systematic review protocol was developed for the meta-analysis, and MEDLINE EBSCO, Google Scholar and EMBASE databases were searched from January 2010 to August 2017. Terms such as Ramadan, Ramadan fasting, diabetes, BMI, body weight, fructosamine, PPG, FPG, *etc*., were used to search appropriate studies in literature.

Study inclusion/exclusion criteria: All studies included in the meta-analysis compared the outcomes before and after RF. Studies were included when at least one of the following outcome indicators had been evaluated: PPG, FPG, HbA_{1c} (%), fructosamine levels and BMI. Details are shown in Figure 1. Studies on patients with T2DM with co-morbidities such as cardiovascular disease were excluded. Only studies with adult participants were considered.

Outcome measures: In this study, results were combined for five outcome indicators: PPG, FPG, HbA_{1c} (%), fructosamine levels and BMI. Among the included

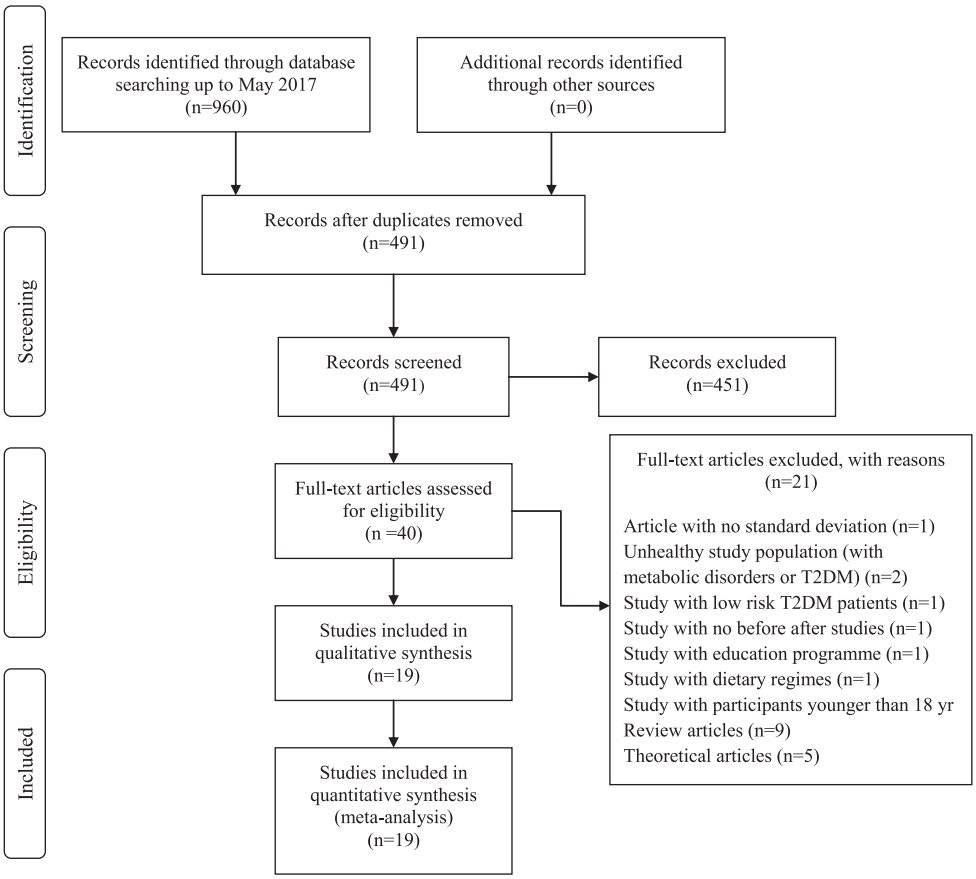

Fig. 1. PRISMA flow diagram of search results.

studies, these were the most commonly used outcomes for which results were available.

Data extraction and quality assessment: Authors, publication year, sample size, characteristics of the population studied and outcome measures were recorded. Two authors independently screened the titles, abstracts and keywords to identify eligibility and assessed methodological quality of the included studies and recorded the findings and the studies were included when both agreed. Any disagreement was discussed with a third author. Quality of the paper was assessed based on the Newcastle-Ottawa Scale[12]. All of included studies achieved a score of 7 out of 8 on that scale. All of the outcome variables were continuous, and means and standard deviations were used as descriptive statistics.

Treatment subgroups: All patients with T2DM participating in the studies included in the meta-analysis were given different therapies. To evaluate the effect of different treatment regimens, studies were classified into three different subgroups: single oral antidiabetics (single OAD), multi-OAD and multitreatment (OAD plus insulin or diet modification).

Data analysis: Data analysis was performed using the guideline for statistical methods as described by the Cochrane Collaboration[13]. Random effect models were used to conduct meta-analysis of continuous outcomes to eliminate the effect of heterogeneity on results for all outcomes[14]. A sensitivity analysis was performed to identify studies with poor quality[15]. The earliest, the largest, the smallest and studies with the most contradictory results were excluded sequentially to see how these affected the meta-analysis when included in the sensitivity analysis. Separate funnel plots to assess potential publication bias for individual outcome variables were plotted. Egger regression test[13] to check funnel plot asymmetry was applied using metaphor package in R package v3.5.1 for windows (*https://cran.r-project.org/bin/windows/base/old/3.5.1/*). Meta-analysis results were presented with a forest plot. Since the units for the variables differed between the publications, these were converted into the most commonly used units to be able to combine results. The standardized weighted mean difference (SMD) and 95 per cent confidence intervals (CI) were used as a summary statistic in the meta-analysis to assess the same outcome. SMD can be considered as a uniform scale between 0 and 1 to express intervention effect[14,15]. A SMD less than 0.40 is interpreted as a small effect size, a SMD between 0.40 and 0.70 as moderate and >0.70 as a large effect size[16]. Analysis was performed using RevMan 5.03[17].

Results

The search strategy identified a total of 960 records (Fig. 1). Among the 40 studies identified, 19 publications with 33 independent treatment groups met the study inclusion criteria. Details of all included studies and treatments are given in Table I. A total sample of 2457 patients was included in the meta-analysis. Five of the included studies were performed in Turkey[18-22], and three were multicentered[23-25]. In studies by Almutari[26] and Belkadir[24] younger population was included compared to the rest of the studies. Not all of the study gave gender information, but majority of the studies included both men and women in the study. Duration of fasting varied between 10 and 30 days. Time of measurements for before and after Ramadan was different for each study.

Effect of Ramadan fasting on PPG: Ten studies were included[19,20,22,27] in the meta-analysis to estimate the pooled reduction in PPG after RF versus before RF. A total of 199 participants were analyzed, including 108 participants in the monotherapy and 56 participants in the oral combination therapy subgroup. RF had no significant effect in the monotherapy group [SMD=0.01, 95% CI=(−0.26, 0.28), P=0.94], and no significant difference was observed in the oral combination therapy group [SMD=0.00, 95% CI=(−0.37, 0.37), P=1.000]. The overall pooled SMD for PPG was 0.06, 95% CI=[(−) 0.14-0.26], which was not significant. SMD estimates and their 95 per cent CIs are shown in Fig. 2.

Effect of Ramadan fasting on FPG: Fifteen studies[19,20,22,26-30] reporting estimates for FPG were included. A total of 624 participants were analyzed, including 364 participants in the monotherapy and 135 participants in the insulin combination therapy subgroup. The Figure 3 displays the results of the meta-analysis. FPG values were significantly decreased in single OAD [SMD=0.47, 95% CI=(0.20-0.74), P<0.001], in the multi-OAD group [SMD=0.36, 95% CI=(0.11-0.61), P=0.005] as well as in the insulin combination therapy after Ramadan [SMD=0.65, 95% CI=(0.03-1.27), P=0.04]. Furthermore, the overall result of meta-analysis was significant [SMD=0.48, 95% CI=(0.27-0.70), P<0.001]. There was heterogeneity across studies for FPG (I^2=61%, P=0.001).

Table I. Summary of the study characteristics included in the meta-analysis

First author, year	Country	Age range or mean age±SD (yr)	Male/ female	Main outcome	Duration of fasting (days)	Time of measurements		Subgroups	Treatments	n
						Before Ramadan	After Ramadan			
Yeoh *et al*, 2017[33]	Singapore	57±11	15/14	HbA_{1c} (%), body weight change, blood pressure, TG	>15	Before	Last day	No subgroups	Oral antidiabetic agents alone or insulin therapy + oral antidiabetics	29
Malha *et al*, 2014[30]	USA	57.0±9.6	-	HbA_{1c} (%), hypoglycaemic events, BMI	>15	Before	Last day	A	Metformin + vildagliptin	30
		54.6±9.2	-					B	Metformin + sulphonylurea	39
Karatoprak *et al*, 2013[22]	Turkey	57.4±10.1	19/57*	HbA_{1c} (%), body weight, BMI, PPG	29	15 days	29th day	A	Insulin premix + metformin	12
								B	Insulin long-acting + metformin	13
								C	Metformin	18
								D	Metformin + pioglitazone + acarbose	17
Şahin *et al*, 2013[21]	Turkey	59.93±9.57	-	PPG, FPG, HbA_{1c} (%), body weight, fructosamine	27	Two week before	At the end of Ramadan	No subgroup	Glinides + metformin	88
Almutairi *et al*., 2012[26]	Kuwait	28-67	36/64	FPG, BMI, CRP, MAP	-	-	-	No subgroup	Oral antidiabetics	100
Vasan *et al*, 2012[27]	India	45±9	-	FPG, PPG, body weight, fructosamine, dietary pattern	30	One week before	One week after	No subgroup	Pioglitazone	50
Khan *et al*, 2012[34]	Pakistan	52.8±8.5	38/37	Glucose level, body weight, lipid profile	>20	10 days	seventh day	No subgroup	Oral antidiabetics + insulin	75
Hassanein *et al*, 2011[32]	UK	58.3±13.1	11/12	Hypoglycaemic events, HbA_{1c} (%), body weight	>10	One-six week	≤ six week after	A	Metformin + vildagliptin	23
		57.3±11	15/21					B	Metformin + suphonylurea	36
Khaled & Belbraouet 2009[25]	Multicenter study/Algeria	49±6	0/276	Anthropometric characteristics and nutrient intakes	-	One month before	One month after	No subgroup	Metformin + glimepiride	276
Devendra *et al*., 2009[35]	UK	53.2±9.7	18/34	Body weight, hypoglycaemic event, HbA_{1c}	>15	Two days before	10 days after	A	Metformin + vildagliptin	26
								B	Metformin + gliclazide	26
M'guil *et al*, 2008[31]	Morocco	48-60	58/62*	BMI, HbA_{1c} (%), fructosamine	30	First day	29th day	No subgroup	Gliclazide	110
Cesur *et al*, 2007[20]	Turkey	56.5±9.2	29/20	FPG, PPG, HbA_{1c} (%), fructosamine	-	Two days before	Four days after	A	Glimepiride	21
								B	Repaglinide	18
								C	Glargine	10

Contd...

First author, year	Country	Age range or mean age±SD (yr)	Male/ female	Main outcome	Duration of fasting (days)	Time of measurements		Subgroups	Treatments	n
						Before Ramadan	After Ramadan			
Patel *et al*, 2007[36]	Sultanate of Oman	54.3±11.7	146/188	BMI, sugar intake, food intake, fluid intake	-	At the beginning of Ramadan	At the end of Ramadan	No subgroup	Insulin + oral antidiabetics	334
GLIRA study group, 2005[28]	Lebanon	53.8±9.2	123/109	FPG, HbA_{1c} (%), BMI	-	One week before	At the end of Ramadan	No subgroup	Glimepiride	232
Gustaviani *et al*, 2004[29]	Indonesia	52.6±8	10/14	BMI, FPG, fructosamine	-	One week before	Two week after	No subgroup	Repaglinide	24
Sarı *et al*, 2004[19]	Turkey	57.79±7	-	BMI, PPG, FPG, HbA_{1c} (%), fructosamine	-	-	-	A	Glimepiride	23
								B	Gliclazide	17
Mafauzy, 2002[23]	Multicenter study/ Malaysia/UK/ France/Saudi Arabia	52.7±7.4	87/29	FPG, HbA_{1c} (%), BMI	-	At the beginning of Ramadan	At the end of Ramadan	A	Repaglinide	116
		54.5±6.9	82/37					B	Glibenclamide	119
Uysal, 1998[18]	Turkey	55	11/30	HDL, LDL, HbA_{1c} (%), BMI	-	Two week before	Last week of Ramadan	No subgroup	Diabetic diet or single or combined oral anti-diabetics	41
Belkhadir *et al*, 1993[24]	Multicenter study/Morocco	33-80	391/198*	Fructosamine, HbA_{1c} (%), body weight	-	One day before	One day after	A	Glibenclamide	78
								B	Glibenclamide	173
								C	Glibenclamide	95
								D	Glibenclamide	87
								E	Glibenclamide	101

*Mismatch in total number of patients is due to dropout. SD, standard deviation; HbA_{1c}, glycated haemoglobin; TG, triglyceride; BMI, body mass index; PPG, post-prandial plasma glucose; FPG, fasting plasma glucose; CRP, C-reactive protein; MAP, mean arterial pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein

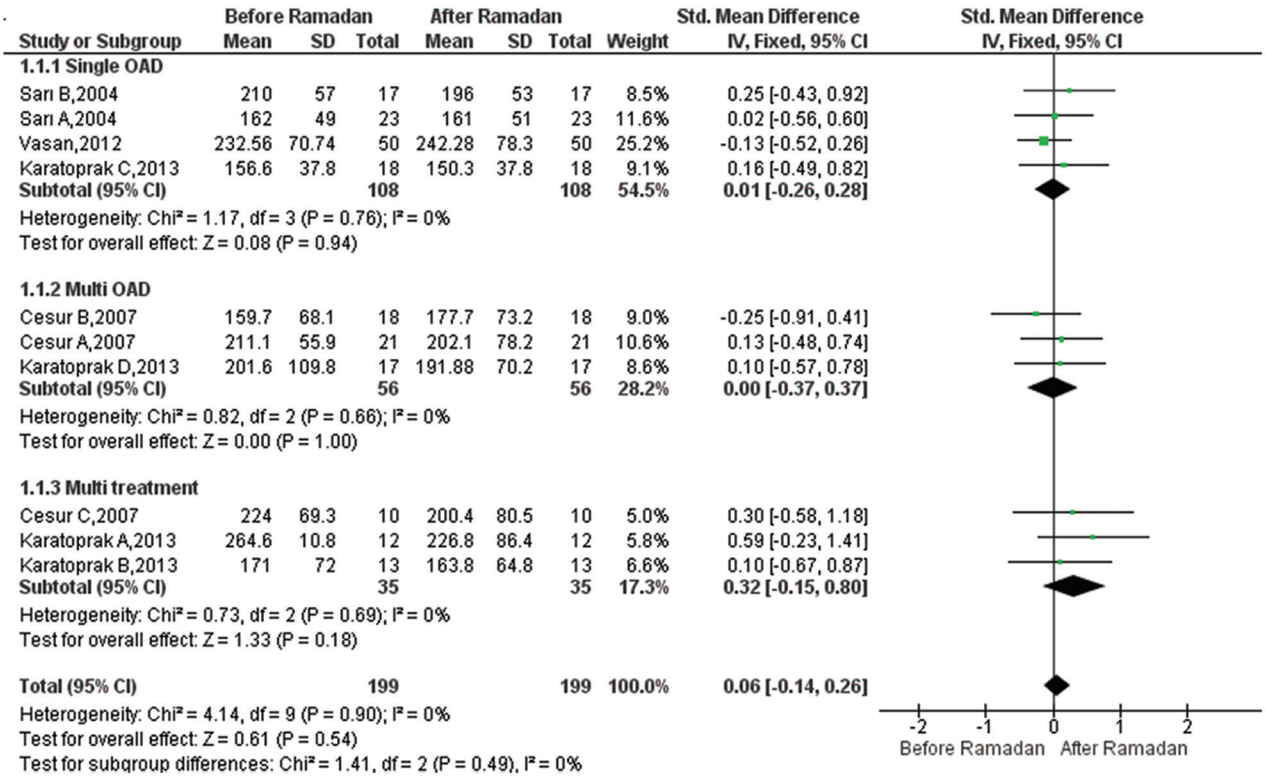

Fig. 2. Forest plot for pre-post Ramadan changes in post-prandial plasma glucose (mg/dl).

Effect of Ramadan fasting on HbA$_{1c}$: A total of 22 studies[18-20,22,24,28,30-33] provided data for the meta-analysis for HbA_{1c} (%) change (1173 participants, 884 in single OAD, 254 in multi OAD and 35 in multitreatment). In the subgroup analysis, there was no significant difference in monotherapy group [SMD=0.03, 95% CI=([−]0.23-0.28), *P*=0.84] and oral combination therapy group [SMD=0.18, 95% CI=([−]0.29-0.65), *P*=0.45]. However, in multi-OAD subgroup, small significant reduction was observed [SMD=0.26, 95% CI=(0.03-0.49), *P*=0.03]. The overall results of random effects model showed that RF did not lead to significant changes in HbA_{1c} (%) levels [SMD=0.13, 95% CI=([−]0.04-0.30), *P*=0.13] (Fig. 4). There was heterogeneity across studies for HbA_{1c} (%) (I^2=71%, *P*=0.01), but there was no difference between subgroups (*P*=0.72).

Effect of Ramadan fasting on fructosamine: Fifteen studies[19,20,23,24,27,29,31] were included in the meta-analysis to estimate the pooled changes in fructosamine after RF compared to before RF. A total of 998 participants were analyzed to evaluate changes in fructosamine levels. Most of the participants received monotherapy (n=943). RF had no significant effect [SMD=(−)0.08, 95% CI=([−]0.24, 0.08), *P*=0.320]. SMD estimates and their 95 per cent CIs are shown in Fig. 5. There was heterogeneity across studies for fructosamine (I^2=65%, *P*=0.001).

Effect of Ramadan fasting on body mass index: Nine[18,26,27,30,31,33-36] studies representing T2DM population of 959 participants reported BMI scores before and after RF. Overall, meta-analysis results of the random effects model showed marginally significant reduction in BMI levels compared to pre-Ramadan levels as shown in Fig. 6 [SMD=0.09, 95% CI=([−]0.00-0.18), *P*=0.06]. Furthermore, in the multi-OAD group, there was a significant decrease in BMI values [SMD=0.18, 95% CI=(0.04-0.31), *P*=0.01].

Discussion

One major finding of our meta-analysis was the reduction in the HbA_{1c} (%) and FPG in the multi-OAD subgroup after Ramadan. In addition to these glycaemic parameters, BMI values were lower after Ramadan in this subgroup. Another meta-analysis on healthy controls also reported significant decrease in body weight after RF[6]. Body weight reduction might have led to improvement in these glycaemic parameters. Norris

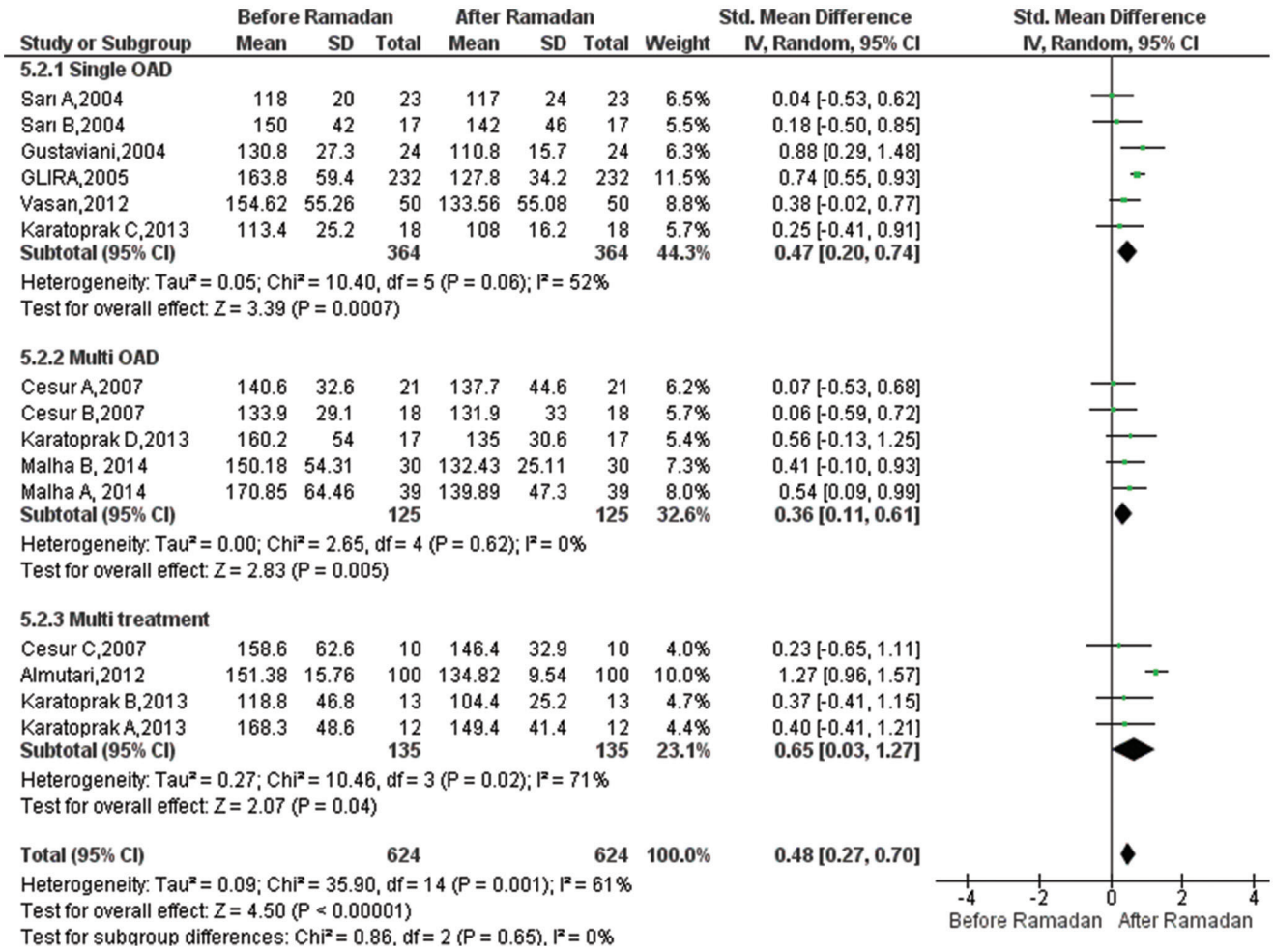

Fig. 3. Forest plot for pre-post Ramadan changes in fasting plasma glucose (mg/dl).

et al[37] showed that relatively modest weight loss was significantly associated with improvement in FPG and HbA_{1c}. Fujioka[38] showed that even the intention to lose weight, without significant success, improved outcomes in patients with diabetes and moderate weight loss had positive effects on metabolic control. However, another meta-analysis examining non-pharmacological weight loss in adults with T2DM did not report significant changes in HbA_{1c}[39]. Another meta-analysis which assessed the benefit of low calorie diet programmes in obese patients reported dramatic reductions in FPG values after two weeks and relative improvement in FPG over the course of a single week, when three per cent decrease was achieved in body weight[40]. Overall results of our meta-analysis also showed significant FPG reductions after Ramadan and overall BMI result was marginally significant. We did not find a significant FPG reduction in the single OAD group. Fasting patients consume substantial amounts of sugary foods and carbohydrate-rich meals during non-fasting hours[5]. Therefore, monotherapy alone for the treatment of diabetes may not be sufficient for FPG control.

Since smoking is not permitted during RF, there is a consequential reduction in smoking and tobacco consumption among fasting diabetic patients. Another explanation for the improvement in FPG and HbA_{1c} (%) could be cessation or reduction of smoking during Ramadan. In healthy young males, an increased insulin resistance was observed in acute smokers[41]. Other studies showed that smoking reduced insulin-mediated glucose uptake by 10-40 per cent when compared to non-smokers[42,43]. Other studies showed a positive association between HbA_{1c} and total smoking exposure as measured by pack-years[44,45]. One of the reasons for positive outcomes of our meta-analysis could be increased treatment adherence during Ramadan. It has been shown that in most of the countries, non-

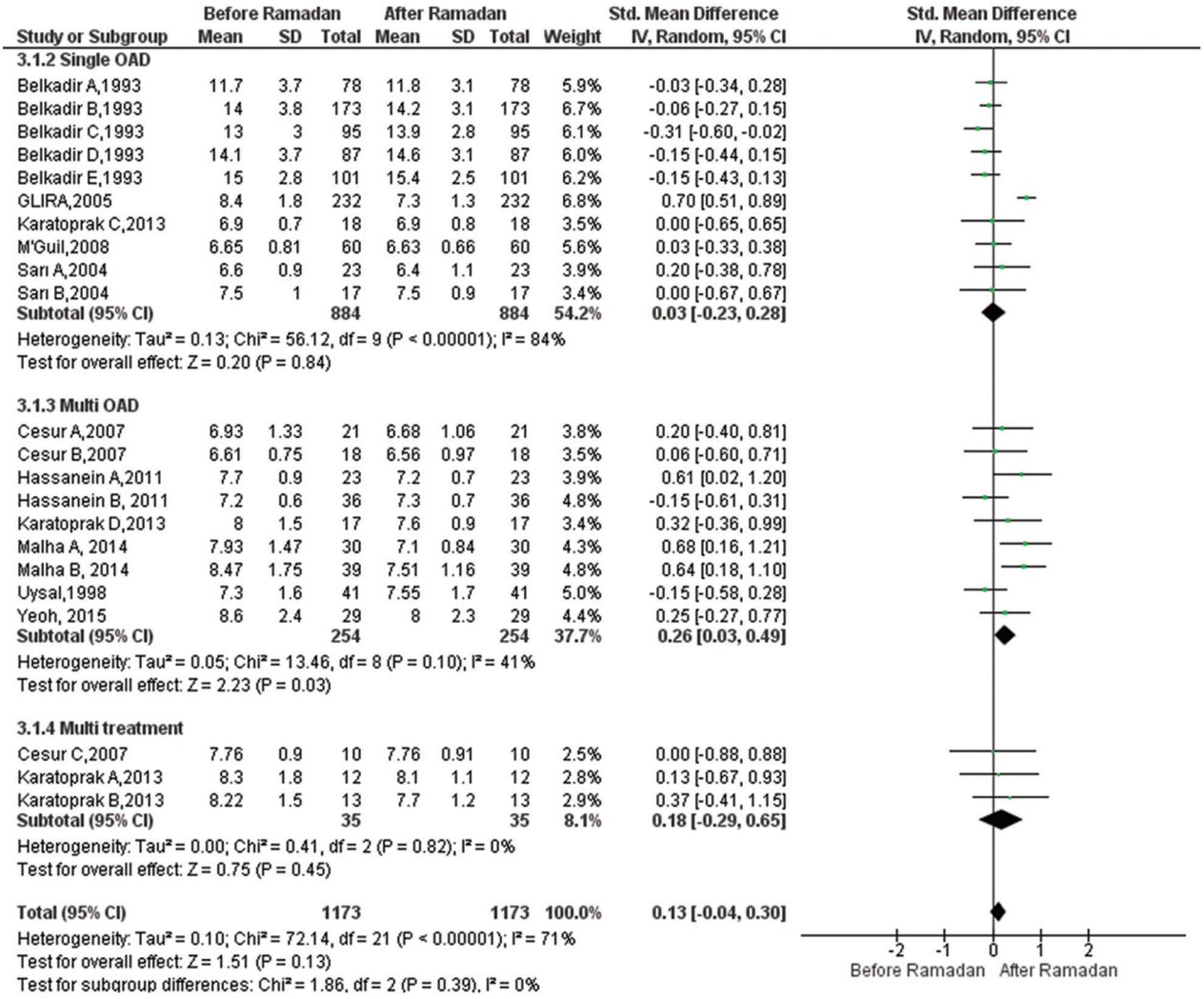

Fig. 4. Forest plot for pre-post Ramadan changes in glycated haemoglobin (%).

adherence rates are surprisingly high during RF[46-48]. However, the VIRTUE study enrolling 1333 patients from 10 countries reported high treatment adherence during Ramadan, with low or similar number of missed doses compared to other months[49].

The sensitivity analysis showed similar SMDs for all of the outcomes (Table II). For fructosamine, HbA_{1c} (%) and FPG significant heterogeneity were detected among included studies. Not all of the included studies followed the same duration of fasting (Table I). Hence, duration of fasting may be one of the reasons for heterogeneity. Egger regression analysis showed no publication bias for PPG (P=0.068), FBG (P=0.802), BMI (P=0.622) and fructosamine (P=0.950). For HbA_{1c} (%), publication bias was detected (P=0.015).

Our study had several limitations. Although studies with co-morbidities were excluded, it was very difficult to include only those cases of diabetes without co-morbid conditions, and most of the studies did not follow similar inclusion criteria. The reported rates of hypoglycaemic and hyperglycaemic and hyperglycaemic rate events vary between 3.7 and 33.3 per cent[18,19,22]. Since only a small number of studies reported these outcomes, we could not include them in our meta-analysis. Another limitation of our study was related to the fact that most of the included studies investigated the impact of RF just after Ramadan; therefore, sustainability of positive outcomes could not be evaluated.

In conclusion, our meta-analysis showed that RF was not associated with any significant negative effects on PPG and fructosamine levels. However, BMI and FPG and HbA_{1c} (%) were positively affected by RF. Although RF showed positive effects on certain

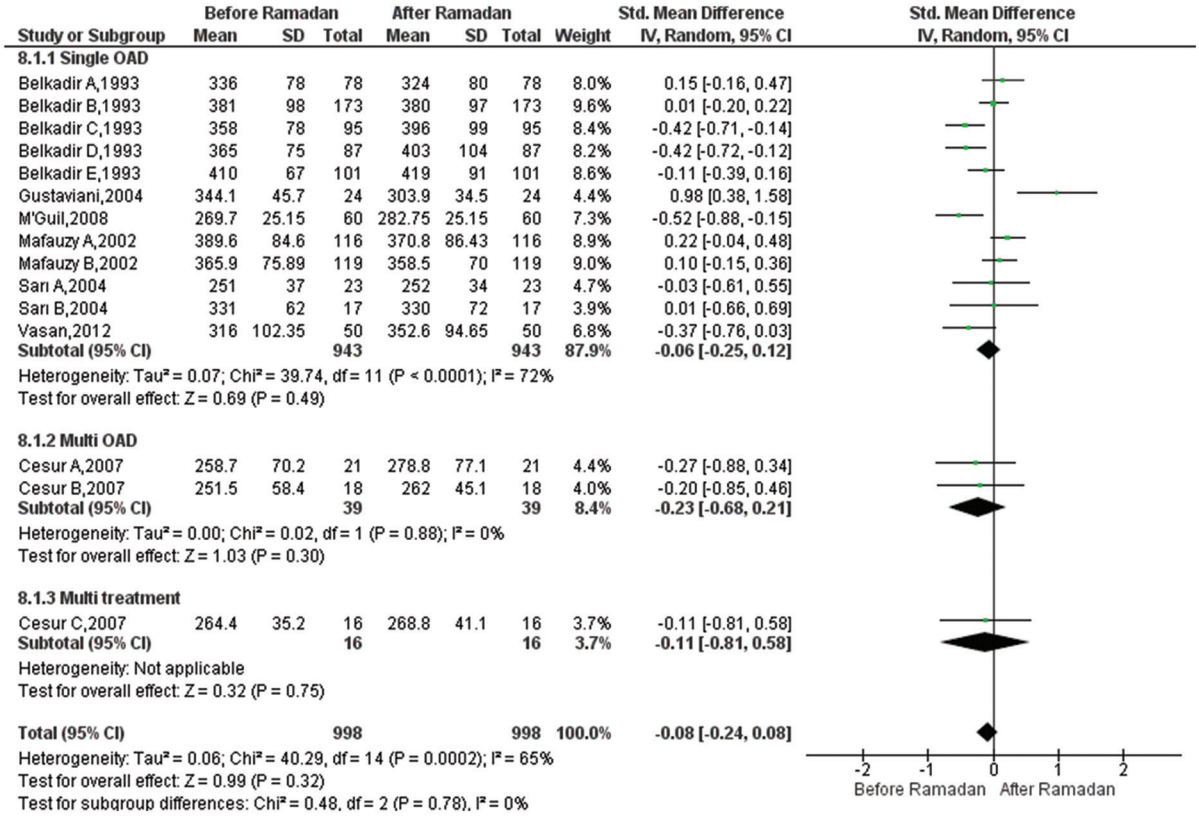

Fig. 5. Forest plot for pre-post Ramadan changes in fructosamine.

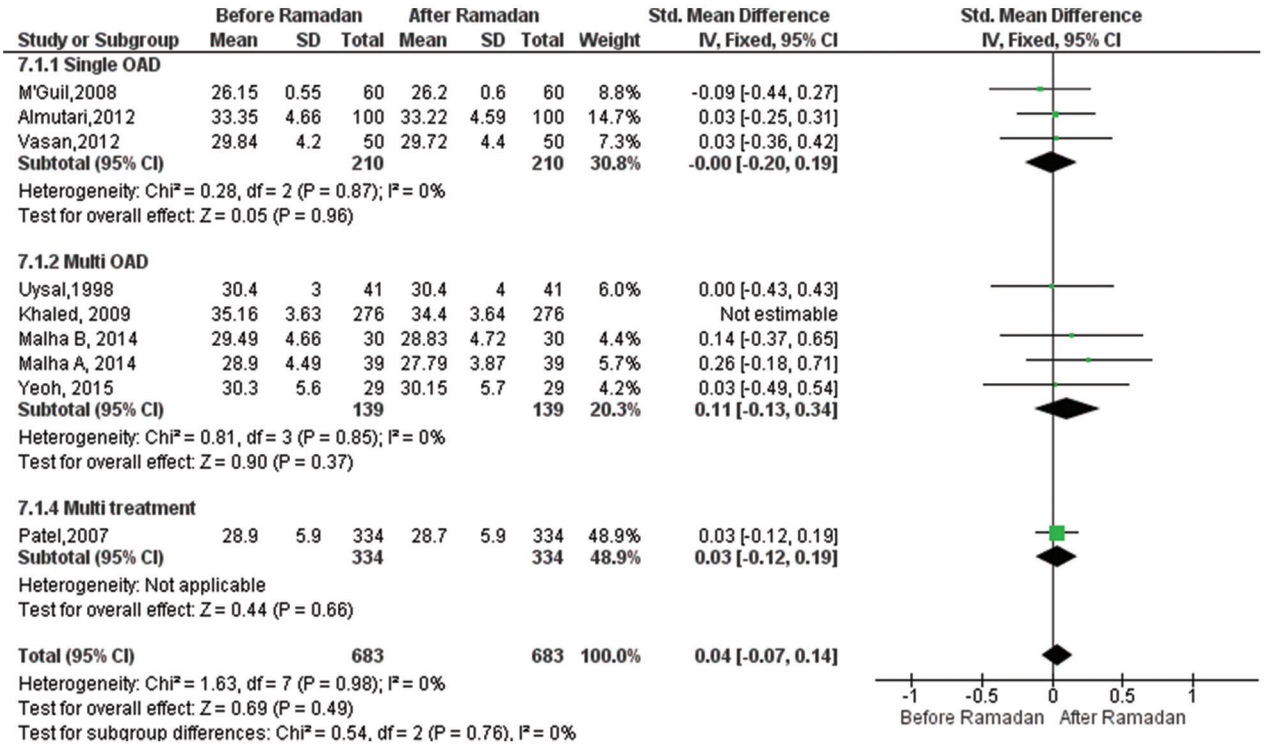

Fig. 6. Forest plot for pre-post Ramadan changes in body mass index.

Table II. Result of sensitivity analysis

Outcome	Effect size	Heterogeneity		Sensitivity analysis			
		I^2 (%)	*P*	Excluding the largest	Excluding the smallest	Excluding the earliest	Excluding studies with the most contradictory results
PPG (mg/dl)	0.06 (−0.14-0.26)	0	0.900	0.13 (−0.10-0.35)	0.03 (−0.17-0.23)	0.05 (−0.17-0.27)	0.09 (−0.11-0.30)
FPG (mg/dl)	0.48 (0.27-0.70)	61	0.001	0.44 (0.20-0.69)	0.49 (0.28-0.71)	0.54 (0.32-0.76)	None
HbA_{1C} (%)	0.13 (−0.04-0.30)	71	0.001	0.05 (−0.07-0.17)	0.13 (−0.04-0.30)	0.14 (−0.03-0.32)	0.16 (−0.01-0.32)
BMI	0.09 (−0.00-0.18)	0	0.810	0.04 (−0.07-0.14)	0.08 (−0.01-0.18)	0.09 (−0.00-0.18)	0.04 (−0.07-0.14)
Fructosamine	−0.08 (−0.24-0.08)	65	0.001	−0.09 (−0.27-0.09)	−0.08 (−0.25-0.09)	−0.03 (−0.27-0.22)	−0.05 (−0.21-0.11)

HbA_{1c}, glycated haemoglobin; TG, triglyceride; BMI, body mass index; PPG, post-prandial plasma glucose; FPG, fasting plasma glucose

outcomes, one should consider the limitations of the study and confounders while interpreting the results.

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***Conflicts of Interest*:** None.

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For correspondence: Dr Seval Kul, Department of Biostatistics, Faculty of Medicine, Gaziantep University, Şahinbey, 27310, Gaziantep, Turkey
e-mail: sevalkul@gantep.edu.tr