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Abstract

Introduction: Restriction in meal timing has emerged as a promising dietary approach for the management of obesity and dysmetabolic diseases. The present systematic review and meta-analysis summarized the most recent evidence on the effect of time-restricted feeding (TRF) on weight-loss and cardiometabolic variables in comparison with unrestricted-time regimens.

Methods: Studies involving TRF regimen were systematically searched up to January 2019. Effect size was expressed as weighted mean difference (WMD) and 95% confidence intervals (CI).

Results: A total of 11 studies, 5 randomized controlled trials and 6 observational, were included. All selected studies had a control group without time restriction; hours of fasting ranged from 12-hrs until 19-hrs and study duration from 4 to 8-weeks. Most studies involved the Ramadan fasting. TRF determined a greater weight-loss than control regimens (11 studies, *n*=485 subjects) (WMD: -1.07kg, 95%CI: -1.74 to -0.40; p=0.002; I^2=56.2%), unrelated to study design. The subgroup analysis showed an inverse association between TRF and fat free mass in observational studies (WMD: -1.33 kg, 95%CI: -2.55 to -0.11; p=0.03; I^2=0%). An overall significant reduction in fasting glucose concentrations was observed with TRF regimens (7 studies, *n*=363 subjects) (WMD: -1.71 mg/dL, 95%CI: -3.20 to -0.21; p=0.03; I^2=0%), above all in trials (WMD:-2.45 mg/dL, 95%CI: -4.72 to -0.17; p=0.03; I^2=0%). No between-group differences in the other variables were found.

Conclusions: TRF regimens achieved a superior effect in promoting weight-loss and reducing fasting glucose compared to approaches with unrestricted time in meal consumption. However, long-term and well-designed trials are needed to draw definitive conclusions.

Keywords: fasting glucose, observational studies, randomized controlled trials, time restricted feeding, weight loss

Introduction

Obesity is a complex, multifactorial disease, affecting, along with overweight, over a third of adult population worldwide [1,2] with an increasing prevalence [3]. Excess adiposity is an established risk factor for all-cause mortality and a public health burden [4,5]. Lifestyle intervention is the first-line therapy to treat obesity and prevent the associated comorbidity, even if its success is often limited [6]. Recently, temporal regulation of feeding has emerged as an innovative strategy in the approach to obesity and dysmetabolic diseases [7].

Time-restricted feeding (TRF) is a dietary regimen encompassing several specific fasting protocols, which share a fasting period of time each day, ranging from 3 to 21-hours (hrs), either diurnal or nocturnal [8,9]. The most practiced schedule of TRF is Ramadan fasting, a pillar of the Islamic religion, during which healthy adult Muslims do not eat or drink during daylight hours for about 1 month [10]. The length of the fasting ranges between 12-22-hrs, depending on the time of year and the location [11], with the consumption of two meals, one larger after sunset and one lighter before dawn [12]. Ramadan has been reported to reduce weight, body fat [13,14], low-density lipoproteins (LDL), total cholesterol [14,15], but increase fasting glucose [15,16]. Previous meta-analyses of studies on the effects of Ramadan fasting confirmed consistent weight and fat mass (FM) loss and improvement in metabolic markers in healthy Muslims [13,17,18], especially in subjects with overweight or obesity [13]. Indeed, most of the studies included did not have a control group. The health-specific benefits of other TRF regimens are heterogeneous due to the hours of fasting/feeding, food choices, personal habits and health status. Beneficial effects on mood disorders, lipids profile, body weight, fasting glucose, cardiometabolic and oxidative stress parameters have been observed with other TRF schedules, both religious [19,20] and not [21–23].

Additionally, the timing of meals could impact on body weight regulation [24,25]. Delaying feeding later in the evening might be disadvantageous, due to a desynchrony between central and peripheral circadian clocks [26,27], potentially affecting gut microbiota composition as well as gastrointestinal function and metabolism [28].

To the best of our knowledge, an overall evaluation of the impact of TRF on multiple metabolic variables, as well as of the benefits of the different TRF regimens is at present lacking. The aim of this systematic review and meta-analysis was therefore to assess the effects of TRF regimens on weight change (primary outcome) and variations in other anthropometric and metabolic variables (secondary outcomes) when compared to regimens with unrestricted time of food intake (controls).

Patients and Methods

This review was conducted following the main items of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [29].

Search strategy

The following electronic databases were queried using a combination of search terms until the 31th of January 2019: PubMed (National Library of Medicine), the TRIP database, the Cochrane Library, EMBASE, and Cumulative Index to Nursing and Allied Health Literature (CINAHL). The construction of the search strategy was performed using database specific subject headings and keywords. Both medical subject headings (MeSH) and free text search terms were employed. Restrictions to human studies were placed.

The search terms included combinations of “time restricted feeding” or “time restricted eating” or “time restricted fasting” or “time restricted diet” or “time restricted meal”, and weight loss, weight gain, fat mass, obesity, insulin, insulin-resistance, insulin sensitivity, type 2 diabetes mellitus (T2DM), cholesterol, triglycerides and blood pressure (free-term

and MESH as possible) [**Additional file-1**]. These search strategies were implemented by hand searching the references reported by all the included studies and systematic reviews on this topic.

Study selection

We included studies with the following characteristics: 1) controlled studies with both randomized (RCTs) and non-randomized (observational) designs; 2) intervention group with a daily fasting period ≥12-hrs but <24-hrs; 3) control groups following a dietary regimen without temporal restriction; 4) study duration ≥4 weeks; 5) ad libitum or controlled intakes during daily feeding window; 6) age of participants >18 years; 7) healthy volunteers or patients with chronic diseases not impacting on outcomes; 8) including changes in body weight as one of the study's outcome.

We excluded studies with the following characteristics: i) lacking a control group; ii) not including body weight as an outcome and/or lacking sufficient information on weight change; iii) including intermittent or periodic fasting/energy restriction; iv) including dietary regimens without temporal restriction in the time of food consumption; v) including participants with acute or chronic diseases impacting on outcomes (e.g. cancer, intestinal bowel disease, kidney/liver chronic disease, major psychiatric conditions, etc); vi) involving subjects <18 years old.

Two authors (MP, SB) independently screened the publications identified in the search and retrieved full texts from potentially relevant abstracts. If discrepancies about inclusion or exclusion of studies were present, consensus was reached by consultation with a third author (IC).

Outcomes

The primary outcome of this systematic review and meta-analysis was comparing changes in body weight between TRF regimens and controls without time-restriction in food consumption. Secondary outcomes were changes in body mass index (BMI), waist circumference, fat mass (FM), free fat mass (FFM), arterial blood pressure, blood values of total cholesterol, HDL and LDL-cholesterol, triglycerides, fasting glucose, fasting insulin, glycated hemoglobin (HbA1c) and the Homeostasis Model Assessment - Insulin Resistance (HOMA-IR) index.

Data collection and extraction

The information extracted from each included study were: 1) first author name and year of publication; 2) study design; 3) inclusion criteria of participants; 4) study duration; 5) number of subjects enrolled in each arm; 6) type of intervention; 7) age; 8) gender; 9) anthropometric variables of participants (weight, BMI, waist circumference); 10) body composition (FM and FFM); 11) systolic (SBP) and diastolic blood pressure (DBP); 12) blood concentrations of fasting glucose, HbA1c, fasting insulin, total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides; 13) HOMA-IR.

Risk of bias assessment

The validity of the studies was independently assessed by two authors (MP, SB) using two tools: 1) the "Risk of bias" tool developed by the Cochrane Collaboration for RCTs [30] and 2) the 'Risk Of Bias in Non-randomized Studies of Interventions' (ROBINS-I) tool for evaluating risk of bias in estimates of the comparative effectiveness of interventions from studies not using randomization to allocate individuals to comparison groups [31]. The possible disagreements were resolved by consensus, or with consultation with a third author (IC).

Data synthesis

Data synthesis was carried out for the outcomes that were reported in at least 3 studies. The pooled effect sizes were expressed as weighted mean differences (WMD) and 95% confidence interval (CI) of the mean outcome values measured at the end of follow-up between TRF and control arms in both observational and RCT studies. The mean difference of changes from baseline was estimated for each study based on the reported baseline and follow-up measurements. If the standard deviation for change from baseline was not shown, we imputed missing values assuming a within-patient correlation from baseline to follow-up measurements of 0.8 as suggested in the Cochrane handbook [32]. If mean differences on change from baseline between groups have been already estimated [33–35], those data were considered.

Random-effects models, stratified according to the study design (RCTs *vs* observational studies), were applied to provide a summary estimate. Inter-study heterogeneity was assessed using Cochrane Q statistic and quantified by I^2 test [36]. To evaluate the influence of each study on the overall effect size, sensitivity analysis was conducted using the one-study remove (leave-one-out) approach.

Meta-regression analyses were conducted to assess the association between the calculated WMD in body weight with the number of fasting hours, the weeks of TRF duration, and BMI of participants of the included studies. Finally, potential publication bias was explored using visual inspection of funnel plot asymmetry and Egger's weighted regression tests.

Meta-analyses were performed by using the Stata Metan package (Stata Statistical Software, Release 13; StataCorp LP, College Station, TX); meta-regressions and Egger's weighted regression tests for publication bias were performed using the metafor package (version 2.1-0) for R (version 3.5.2, R Foundation for Statistical Computing, Vienna, Austria).

Results

Included studies

The initial literature search identified 623 records (**Figure 1**). After removing duplicates, 260 records were screened, and, after excluding articles not meeting the inclusion criteria, 17 records were assessed for eligibility. After further analysis and quality assessment, 11 studies were selected for the systematic review and meta-analysis, including a total number of 452 subjects, of whom 290 were males (**Table 1**). The largest study recruited 147 subjects [37] while the smallest 8 subjects [38]. Participants were: healthy individuals [33–35,39–42], resistance training men [43], patients with overweight/obesity and prediabetes [38], patients with non-alcoholic fatty liver disease (NAFLD) [44] and with T2DM [37]. The demographic and clinical characteristics of the participants of the included studies are shown in Table 1.

Five of the included studies were trials: cross-over [38-39] or parallel-arms randomized controlled trials [34-35,43]. Five studies were observational prospective studies [33,40–42,44] and 1 was an observational retrospective study [37]. All the studies included an intervention group with a TRF regimen and a control group with unrestricted time of food intake. The duration of the studies varied from 4 weeks [33,37,40–42,44], to 5 weeks [38], 6 weeks [34] and 8 weeks [35,39,43].

Included studies were conducted in the USA [38-39,43], Iran [40,44], Turkey [37], Italy [35], Canada [41], Denmark [33] Germany [42] and UK [34], between 2003 and 2018.

Dietary intervention

The hours of fasting varied among studies. All the observational studies were performed during Ramadan fast and included 12-hrs [40], 14-hrs [33], 15-16-hrs [44], 16.5-hrs [37], 18-hrs [41] and 19-hrs [42] of daytime fasting. In trials, participants were submitted to 16-hrs [35], 18-hrs [38] or 20-hrs [39,43] of fasting. Betts [34] did not report the fasting duration.

The exact time-period of food intake during the night was not reported in any of the observational studies. In the RCTs, the duration of the feeding windows was complementary to fast. In 1 RCT, an early TRF of 6-hrs (8:00 am to 2:00 pm)

with an extended night fast from the afternoon onwards was scheduled [38]. All the other trials extended the night fast in the first part of the day, delaying the feeding period in the evening/night [34-35,39,43], with the start of eating at 12:00 pm [34], at 1:00 until 8:00 pm [35], at 5:00 until 9:00 pm [39] or at 4:00 until 12:00 pm (in a self-selected 4-hrs period of time) [43]. Both in observational studies and RCTs, the control groups consumed 3 meals in the habitual period of time (usually ≥12-hrs).

In the observational studies, no specific dietary recommendations were given, except for 1 study where both TRF and control groups were instructed to follow a low-calorie, low-fat diet [40].

Dietary intakes were reported in 4 observational studies [33,40-41,44] and in 4 RCTs [34-35,39,43]. In the observational studies, a lower caloric intake was reported in the TRF groups, ranging from ~200 kcal/day [33,40,44] to ~350 kcal/day [41]; the between-group difference resulted statistically significant in 2 studies [40,44]. In the RCTs, either a lower energy intake in TRF participants (ranging from ~175 kcal/day [35] to ~470 kcal/day [34,43]) or no between-group differences [39] were reported.

Dietary Compliance and dropouts

Dietary intakes and compliance to the assigned meal diet were assessed by 24-h recall [40,44], 3-days [41], 4-days [43], 7-days food records [35], weighed food diaries during the first and last week of the intervention [34] or detailed recorded dietary intake using a kitchen scale via Internet for 3-days [33]. In 2 studies, meals were provided [38-39]; dietary adherence was either evaluated by observing the consumption of the meals and reviewing daily questionnaire by a registered dietitian [39] or not measured or enforced [38]. In 2 studies, no intake assessment was performed [37,42].

At enrolment, the total number of subjects included were 349 in observational studies and 128 in RCTs. Two observational studies [41-42] and 3 RCTs [38-39,43] reported dropouts. Overall, in the observational studies, 5 participants dropped-out, 4 from TRF groups [41-42] and 1 control [42]. In the RCTs, 20 participants dropped out, 4 from TRF groups [43], 8 from controls [38,43], and 8 did not completed the crossover RCTs [38-39]. The number of the analyzed participants was therefore 452, 344 from observational studies and 108 from RCTs.

Risk of bias assessment

The risk of bias for the RCTs was shown in **Table 2**. Two of the analyzed trials [39,43] were characterized by the lack of information about the randomization procedures**.** If blinding of participants was not feasible owing to the nature of the interventions, data about blinding of the personnel who performed the laboratory or statistical analyses was often unknown, except for 1 study [35]. Incomplete outcome data due to the high rate of dropouts were reported for 3 trials [38-39,43].

Most trials appeared to be free of selective outcome reporting and of other sources of bias, except for one study [43] where between-group difference in the dietary records and subjective measurements were present.

The risk of bias for the observational studies is reported in **Table 3**. Most of the evaluated risks of bias were moderate/serious, therefore, most studies were at high risk of bias. Four studies were at serious risk of bias, because of between-group differences in the baseline clinical characteristics [40,44], bias in the selection of the groups [37], or the measurement of blood parameters only in the TRF group [41].

Qualitative synthesis

Body weight changes were reported in all the included studies [33-35,37-44]. Six studies, 4 observational [33,40,41,44] and 2 RCTs [35,39] reported a significant reduction of body weight in the TRF group when compared to time-unrestricted

regimens, ranging from a minimum of ~1 kg [33,35] to a maximum of ~2 kg [41,44]. The other studies reported no between-group weight differences [34,37-38,42-43]. Four observational studies [33,37,40-42,44] reported a significant BMI reduction in the TRF groups too [33,40-41,44]. Waist circumference values were reported in 2 studies, 1 observational [44] and 1 RCT [34]. TRF led to the reduction in waist circumferences when compared to controls (-0.95±0.73 *vs* -0.036±0.50 cm; $p<0.001$) in the observational study, while no between-group difference was reported in the RCT [34]. Seven studies, 3 observational [33,41-42] and 4 RCTs [34-35,39,43] assessed body composition: 3 studies [35,39,41] reported a significant reduction in FM in the TRF groups, while no study reported remarkable between-group changes in FFM. Seven studies, 3 observational [33,37,44] and 4 RCTs [34-35,38-39] analyzed blood glucose levels: TRF regimens were associated with a significant fasting glucose reduction in 2 studies [33,35]. No between-group difference in HbA1c values were found in the 2 observational studies which measured this laboratory parameter [33,37]. Fasting insulin was reported in 5 studies, 2 observational [33,44] and 3 RCTs [34-35,38]: a statistically significant between-group reduction in the TRF groups was found in 3 studies [35,38,44]. A significant between-group difference in HOMA-IR values was found in 1 study (observational) [44] of the 4 which analyzed this score [33-34,38].

Six studies, 2 observational [33,40] and 4 RCTs [34-35,38-39] measured lipid variables with discordant findings. Two studies reported no between-group differences [33-34]; 1 RCT showed a significant reduction in triglycerides levels in the TRF group [35]; 1 observational study found significant reductions in total cholesterol, LDL-cholesterol and triglyceride with TRF [40]; 1 RCT evidenced a significant increase in fasting triglycerides and total cholesterol after TRF [38]; 1 RCT described a significant increase of total cholesterol, HDL-cholesterol and LDL-cholesterol with the TRF regimens [39].

Five studies, 3 observational [33,41,44] and 2 RCTs [38-39] analyzed arterial blood pressure values. No between-group difference was reported in the observational studies, while the RCTs reported significant between-group differences in both SBP and DBP in the TRF groups, with either lower [38] or increased [39] values with respect to unrestricted regimens.

Meta-analysis

Data synthesis was performed for the outcomes reported in at least 3 studies, therefore data relative to waist circumference and HbA1c were not pooled.

Weight loss

Overall, pooled data from 11 studies (485 subjects) showed a consistent effect of TRF on weight loss (WMD: -1.07kg, 95%CI: -1.74 to -0.40; $p=0.002$; $I^2=56.2\%$). Specifically, the random-effect analysis for subgroups based on study design (observational versus RCTs) showed a significant reduction in weight loss, larger in the observational studies (WMD: -2.05kg, 95%CI: -2.74 to -1.36; $p<0.001$; $I^2=0\%$) than in RCTs (WMD: -0.38kg, 95%CI: -0.71 to -0.05; $p=0.026$; $I^2=0\%$) (**Figure 2**). The estimated effect size for the impact of TRF on weight loss was robust in the leave-one-out sensitivity (data not shown).

Other anthropometric measures

BMI data were reported in 7 observational studies (387 subjects) [33,37,40–42,44] showing a robust effect of TRF regimens (WMD: -0.73 kg/m^2; 95%CI -1.05 to -0.42; $p<0.001$; $I^2=0\%$) compared to controls (data not shown).

Body composition was measured by different methods: bioelectrical impedance analysis (BIA) [39,42], hydrodensitometry [41], Dual-energy x-ray absorptiometry (DXA) [33–35,43] and magnetic resonance imaging scans

[33]. Six studies (181 subjects), 2 observational [41,42] and 4 RCTs [34,35,39,43], reported changes in FM, while 7 studies (201 subjects), 3 observational [33,41,42] and 4 RCTs [34,35,39,43] in FFM. Overall, random effect analysis showed no differences between groups in FM (WMD: -0.62 kg, 95%CI: -1.54 to 0.29; p=0.18) as well as in FFM (WMD: -0.38 kg, 95%CI: -1.04 to 0.28; p=0.25) as presented in **Figure 3** (a and b, respectively). However, the subgroup analysis showed a small effect of TRF on FFM in the observational group (WMD: -1.33 kg, 95%CI: -2.55 to -0.11; p=0.03; I^2=0%), as shown in Figure 3b. Those results did not change after performing sensitivity analyses for FFM, while the estimated effect of TRF on FM was sensitive to the study by Betts et al. [33], producing an effect size of -1.23 kg; 95% CI: −2.39 to -0.07 (p = 0.04).

Cardiometabolic biomarkers

Pooled data for glucose, insulin and HOMA-IR values are shown in **Figure 4** (a, b, c; respectively). Changes in fasting glucose were reported in 7 studies (363 subjects), 3 observational [33,37,44] and 4 RCTs [34,35,38,39], showing a significant overall effect of TRF on glucose reduction (WMD: -1.71 mg/dL, 95%CI: -3.20 to -0.21; p=0.03; I^2=0%). The results on fasting glucose were mainly supported by the RCTs (WMD: -2.45 mg/dL, 95%CI: -4.72 to -0.17; p=0.03; I^2=0%), as shown in the separated analyses. The estimated effect size for the impact of TRF on glucose was sensitive to the study by Stote et al. [39], providing an effect size equivalent to −1.24 mg/dl; 95% CI: −2.92 to 0.44; p = 0.15). Fasting insulin values were reported respectively in 5 studies (186 subjects), 2 observational [33,44] and 3 RCTs [34,35,38]. HOMA-IR data were available in 4 studies (152 subjects), 2 observational [33,44] and 2 RCTs [34,38]. Random-effect analyses showed no overall differences either on insulin (WMD: -0.34 µIU/mL, 95%CI: -1.04 to 0.37; p=0.35) or HOMA-IR (WMD: -0.05 mmol/L×µIU/mL, 95%CI: -0.28 to 0.18; p=0.67) changes in the TRF groups when compared to the controls, with consistent results in both subgroup and sensitivity analyses.

Total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides were reported by 6 studies (171 subjects), 2 observational [33,40] and 4 RCTs [34-35,38-39], and the pool data are presented in **Figure 5** (a, b, c and d; respectively). Analyses did not show differences between TRF and control groups on total cholesterol (WMD: 2.43 mg/dL, 95%CI: -10.5 to 15.4; p=0.71), HDL-cholesterol (WMD: 0.76 mg/dL, 95%CI: -0.98 to 2.49; p=0.39, LDL-cholesterol (WMD: -0.44 mg/dL, 95%CI: -9.21 to 8.32; p=0.92) and triglyceride concentrations (WMD: -2.09 mg/dL, 95%CI: -19.9 to 15.7; p=0.82). Similarly, no differences were found according to study design (observational and RCT groups). The estimated effect size for the impact of TRF on cholesterol, HDL and LDL was consistent in the sensitivity analysis. The effect of TRF on triglycerides was significant (WMD: −7.98 mg/dl; 95% CI: −15.39 to -0.56; p=0.035) after removing the study of Sutton [38], according to the leave-one-out analysis.

Finally, changes in both SBP and DBP were described in 5 studies (165 subjects), 3 observational [33,41,44] and 2 RCTs [38-39] and reported in **Figure 6** (a and b, respectively). No differences were observed between TRF and control groups in SBP (WMD: -4.09 mmHg, 95%CI: -8.98 to 0.80; p=0.10) and DBP values (WMD: -0.18 mmHg, 95%CI: -4.09 to 3.74; p=0.93). However, subgroup analysis showed a significant effect of TRF on SBP in the observational group only (WMD: -5.31 mmHg, 95%CI: -8.44 to -2.18; p=0.001; I^2=0%). Both SBP and DBP data were consistent with the sensitivity analyses.

Meta-regression

Mixed-effect meta-regression analyses were performed to evaluate the association between weight loss effects of TRF and the number of daily fasting hours, TRF duration (in weeks) and participants' BMI as potential moderator variables (**Figure 7**). Changes in body weight showed no association with the number of fasting hours (0.13 kg per 1 h/day increase;

95%CI:-0.40 to 0.65; p=0.63), the weeks of TRF duration (0.23 kg per 1 week increase ; 95%CI:-0.21 to 0.68; p=0.31) and BMI of the participants (-0.01 kg per 1 point BMI increase; 95%CI:-0.21 to 0.19; p= 0.91).

Publication bias

The presence of potential publication bias on weight changes was explored by using the Egger's linear regression test for funnel plot asymmetry. Results did not show any significant asymmetry (p=0.15) (**Figure 8)**.

Discussion

A significantly higher weight loss and lower fasting glucose values were found in participants to TRF regimens when compared to controls with unrestricted time of food intake. In observational studies, TRF led to a significant reduction of BMI, FFM and SBP, too.

Effects of TRF on weight loss and body composition

Both observational and RCT studies reported a significant reduction in body weight, with a more evident effect in the former (~2 kg less) than in RCTs (~0.4 kg less). A significant reduction in BMI was found in the observational studies only [33,37,40–42,44]. All observational studies assessed the Ramadan fasting and most of them reported a between-group difference in the daily caloric intake, which, even if not always significant from a statistical point of view, might be clinically significant, ranging from ~200 to ~350 kcal/day [33,40-41,44]. Furthermore, the weight reduction seemed to be due to loss in FFM (with a reduction of ~1.3 kg) rather than FM.

TRF regimens in rodent models have shown to be beneficial on body weight and body composition, cardiometabolic markers, cancer progression and aging, leading to increase lifespan [45–47]. In humans, few controlled studies have explored the metabolic effects of the TRF schemes, so most of information derived from observational studies on Ramadan fasting. A recent meta-analysis, including most Ramadan studies on healthy adults, revealed a significant, but transient, reduction in weight, FM and FFM, especially in individuals with excess body fat [13], in accordance with previous meta-analyses [17,18]. Indeed, all previous meta-analyses reported within-group effects, before and after the Ramadan fasting, lacking a comparison with subjects with unrestricted time of food intake.

Weight loss during Ramadan fasting might be due to the lower caloric intake overall consumed. During the TRF regimens, the duration of the fasting period could influence the caloric intakes by limiting the access to food, even if no intentional calorie restriction has been imposed to participants. Indeed, dehydration during the diurnal fasting hours might have played a role in the increased loss of FFM (Figure 3b), being fluid loss more pronounced in individuals with excess adiposity due to their increased glycogen stores [13]. Other authors have hypothesized a more efficient utilization of body fat [18] and a lower absorption of nocturnal meals, due to reduced gastric emptying and blood flow in the night-time [17] to explain the increased FM loss after Ramadan in subjects with overweight/obesity [13]. Indeed, a significantly higher weight (-1.4 kg) and FM (-2.1 kg) loss was observed also between TRF and control groups consuming the same daily caloric intakes [39]. After 4-6-hrs fasting, gluconeogenesis is stimulated and free fatty acids and amino acids are used as substrates for the energy supply [48], but a switch of metabolism towards the preferential use of fat substrates requires more time, depending on individual characteristics [49]. In humans, above all in insulin-resistant individuals, the metabolic shift occurs after a prolonged fasting (≥72-hrs), thus increased fat mobilization to fatty acid beta-oxidation could not be implicated in the effects of the TRF regimens [49].

A possible role of the gut microbiota on the weight loss determined by TRF regimens has been reported in some [50,51], but not all [52] animal studies. The gut bacteria are influenced by diet and circadian rhythms [53,54]. TRF seems to

improve intestinal microenvironment by restoring microbial cyclical fluctuations when feeding is in alignment with physiological patterns [55], leading to a favorable microbial profile, with an increase in the relative abundance of Bacteroidetes and Verrucomicrobia species and a decrease of Firmicutes [50]. Furthermore, strengthened intestinal epithelial tight junctions have been observed during TRF, leading to favorable metabolic status, reduced inflammation, oxidative stress, apoptosis and an overall increased anti-injury capacity [51].

In conclusion, TRF seems to be effective on weight loss, at least in the short term, probably because fewer calories and less liquids are assumed if the timing of the meals is restricted. However, we cannot exclude that other mechanisms, at present documented in animals only, could be implicated in humans, for example an improvement in the gut microbiota pattern.

Effects of TRF on cardiometabolic biomarkers

The reduction in blood fasting glucose (~2 mg/dL less) was statistically significant, but not relevant from a clinical point of view, while changes in insulin, HOMA-IR, and blood lipids did not differ between groups.

Previous reviews and meta-analyses reported discordant effects of Ramadan fasting on cardiometabolic markers, with either improvement in fasting glucose, decrease in total and LDL-cholesterol and triglycerides and increase in HDL-cholesterol or neutral or unfavorable effects on lipid profiles in patients with T2DM [13-14,18,56-57]. Fasting duration, timing of meals and quality of diet could have had a role [14,58].

In RCTs, the timing of the eating window seems to influence the outcomes of TRF both in animals and humans [8,59-60]. Most of the analyzed RCTs extended the night fast in the first part of the day [34-35,39,43], but one, where an eating regimen restricted in the morning was associated with a greater improvement in insulin sensitivity and β-cell responsiveness [38]. Possibly, a TRF schedule in alignment with circadian rhythms elicits beneficial metabolic effects, not solely due to weight loss [38,61-62]. Indeed, in humans, a desynchronization between exogenous (fasting/feeding and sleep/wake) and endogenous circadian cycles impacts negatively on glucose and lipid metabolism, cortisol profile, appetite, blood pressure [63–67], and dysregulates the circadian transcriptome [68]. Increased insulin resistance, lipolysis and oxidative stress were reported at night [69-70]. Furthermore a chronically disturbed circadian rhythm may affect gut microbiota composition and function, and impair metabolism and health [59], promoting glucose intolerance and obesity in mice [71]. Mice are nocturnal animals, therefore, a TRF regimen with feeding during the nocturnal active phase partially restores the gut microbiota cyclical fluctuations [50]. In humans, conversely, TRF might elicit beneficial effects when a diurnal eating window is aligned with the physiological circadian rhythms. This could explain the discordant results relative the metabolic changes after Ramadan fasting, even if almost all studies reported an increased weight loss. Further RCTs with a TRF limited to the first part of the day are warranted to clarify this important topic.

Finally, we found a significant reduction in SBP in observational studies, in accordance with previous systematic reviews [14,56,58]. Possible mechanisms could be the increased weight loss and the higher caloric restriction and dehydration of the TRF groups. A hungry-induced suppression in sympathetic tone inducing a fall in blood pressure has been hypothesized after fasting [58].

Limitations

Many limitations should be recognized. First, both observational studies and RCTs were heterogeneous, with different timing of meals, duration of fasting, feeding protocols and dietary composition. Furthermore, the small sample sizes, being most participants Muslim males, made the results difficult to be generalized. The limited follow-up together with

the methodological problems of many studies were further limitations to be considered. Finally, some outcomes have been evaluated by a limited number of studies.

Conclusion

A TRF promotes weight loss in the short term, probably because the caloric intake was overall reduced. Further larger high-quality RCTs with longer follow-ups are needed to define the impact of meal-time restriction on body composition, metabolic pattern and cardiovascular health.

Conflict of Interest: The authors declare that they have no conflict of interest.

Author contribution: MP participated in the conception of the paper, collection and analysis of the studies, manuscript writing and revision. IC, VP, IG, EG participated in the collection of the references and interpretation, manuscript writing and revision. AE, GC participated in the statistical analyses and interpretation of the results. SB participated in conception of the paper, collection and analysis of the studies, manuscript writing and revision. All authors have read and approved the final manuscript.

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Figure captions

Fig. 1 Flow of the study

Fig. 2 Meta-analysis of the effects of time restricted feeding versus controls on weight loss
MD (mean difference) indicates the mean difference on change from baseline of the TRF vs the control groups. The plotted points are the mean differences and the horizontal error bars represent the 95% confidence intervals. The grey areas are proportional to the weight of each study in the random-effects meta-analysis. The vertical dashed line represents the pooled point estimate of the mean difference. The solid black line indicates the null hypothesis (MD=0).

Fig. 3 Meta-analysis of the effects time restricted feeding versus controls on fat mass (a) and fat free mas (b) values
MD (mean difference) indicates the mean difference on change from baseline of the TRF vs the control groups. The plotted points are the mean differences and the horizontal error bars represent the 95% confidence intervals. The grey areas are proportional to the weight of each study in the random-effects meta-analysis. The vertical dashed line represents the pooled point estimate of the mean difference. The solid black line indicates the null hypothesis (MD=0).

Fig. 4 Meta-analysis of the effects time of restricted feeding versus controls on fasting glucose (a), insulin (b) and HOMA-IR (c) values
MD (mean difference) indicates the mean difference on change from baseline of the TRF vs the control groups. The plotted points are the mean differences and the horizontal error bars represent the 95% confidence intervals. The grey areas are proportional to the weight of each study in the random-effects meta-analysis. The vertical dashed line represents the pooled point estimate of the mean difference. The solid black line indicates the null hypothesis (MD=0).

Fig. 5 Meta-analysis of the effects of time restricted feeding versus controls on total cholesterol (a), HDL- cholesterol (b), LDL-cholesterol (c) and triglycerides (d) values
MD (mean difference) indicates the mean difference on change from baseline of the TRF vs the control groups. The plotted points are the mean differences and the horizontal error bars represent the 95% confidence intervals. The grey areas are proportional to the weight of each study in the random-effects meta-analysis. The vertical dashed line represents the pooled point estimate of the mean difference. The solid black line indicates the null hypothesis (MD=0).

Fig. 6 Meta-analysis of the effects of time restricted feeding versus controls on systolic blood pressure (a) and diastolic blood pressure (b) values
MD (mean difference) indicates the mean difference on change from baseline of the TRF vs the control groups. The plotted points are the mean differences and the horizontal error bars represent the 95% confidence intervals. The grey areas are proportional to the weight of each study in the random-effects meta-analysis. The vertical dashed line represents the pooled point estimate of the mean difference. The solid black line indicates the null hypothesis (MD=0).

Fig. 7 Meta-regression plots
Meta-regression plots of the association between mean changes in body weight with number of fasting hours (a) study duration (b) and participants' BMI (c). The size of each circle is inversely proportional to the variance of change.

Fig. 8 Funnel plot for publication bias detection on weight loss changes
The funnel plot shows the observed mean differences (on the x-axis) against standard errors (on the y-axis). In the absence of publication bias, the plotted points form a funnel shape.