Effects of Orthodox religious fasting versus combined energy and time restricted eating on body weight, lipid concentrations and glycaemic profile

Spyridon N. Karras[a], Theocharis Koufakis[a], Lilian Adamidou[b], Vasiliki Antonopoulou[a], Paraskevi Karalazou[c], Katerina Thisiadou[c], Elina Mitrofanova[d], Hilda Mulrooney[d], Andrea Petróczi[d], Pantelis Zebekakis[a], Kali Makedou[c], Kalliopi Kotsa[a*]

[a] Division of Endocrinology and Metabolism, First Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, AHEPA University Hospital, Thessaloniki, Greece

[b] Department of Dietetics and Nutrition, AHEPA University Hospital, Thessaloniki, Greece

[c] Laboratory of Biological Chemistry, Medical School, Aristotle University of Thessaloniki, AHEPA University Hospital, Thessaloniki, Greece

[d] School of Life Sciences, Pharmacy and Chemistry, Kingston University London, Penrhyn Road, Kingston upon Thames, Surrey, KT1 2EE, United Kingdom

Corresponding Author: Assoc. Professor Kalliopi Kotsa, Division of Endocrinology and Metabolism and Diabetes Center, First Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, AHEPA University Hospital, 1 St. Kiriakidi Street, 54636, Thessaloniki, Greece, email: kalmanthou@yahoo.gr

ABSTRACT

For seven weeks, 37 overweight adults followed a hypocaloric diet based on Orthodox Fasting (OF). A hypocaloric, time restricted eating (TRE) plan (eating between 08:00 to 16:00h, water fasting from 16:00 to 08:00h) was followed by 23 Body Mass Index (BMI)-matched participants. Anthropometric, glycaemic and inflammation markers and serum lipids were assessed before and after the diets. Both OF and TRE groups demonstrated reductions in BMI (28.54 ± 5.45 vs 27.20 ± 5.10 kg/m^2, $p<0.001$ and 26.40 ± 4.11 vs 25.81 ± 3.78 kg/m^2 $p=0.001$, respectively). Following the intervention, the OF group presented lower concentrations of total and low-density lipoprotein-cholesterol, compared with the pre-fasting values (178.40 ± 34.14 vs 197.17 ± 34.30 mg/dl, $p<0.001$ and 105.89 ± 28.08 vs 122.37 ± 29.70 mg/dl, $p<0.001$, respectively). Neither group manifested significant differences in glycaemic and inflammatory parameters. Our findings suggest that OF has superior lipid lowering effects than the TRE pattern.

Key-words: Orthodox fasting; Cardiometabolic markers; Lipids; Insulin resistance; Intermittent fasting; Time restricted eating

Introduction

Accumulating evidence suggests the Mediterranean Diet (MD) as an ideal nutritional model for the prevention of cardiometabolic diseases, including diabetes mellitus (DM) and coronary artery disease (CAD) (Keys et al. 1986; Prinelli et al. 2015). In contrast, western-pattern diets, containing large amounts of saturated fatty acids (SFA) and leading to increased visceral adiposity have resulted in an increasing prevalence of cardiometabolic diseases worldwide, which is expected to become even greater within the next decades (Caputo et al. 2017; Mendola et al. 2018). The contribution of limited physical activity to the obesity pandemic should be also considered, albeit its impact is not well-defined and might be less crucial than that traditionally believed (Muller and Soares 2019). In any case, the complex interactions between genetic, dietary and life-style factors that determine the development of the disorder render the establishment of causal associations challenging.

Orthodox religious fasting (OF) comprises a variation of the typical MD, where fasting and non-fasting periods alternate during the calendar year. It is deeply integrated in the dietary behaviour of Orthodox Christians and is followed by a large proportion of the Orthodox population for prolonged periods (from 120 to 180 days) annually (Persynaki et al. 2017). This nutritional advocacy has been shown to integrate characteristics that promote cardiovascular (CV) health, including energy restriction and optimal effects on lipid concentrations (Sarri et al. 2004). Athonian monks, residing in the monastic community of Athos in Northern Greece, practice a pescatarian OF variation in which meat consumption is not allowed during either fasting or non-fasting days. We have previously demonstrated that the Athonian fasting is characterised by lower energy intake than the typical OF, thus resulting in optimal anthropometric profiles and low insulin resistance among the monks (Karras et al. 2017, 2019).

Ramadan is an alternative type of complete, intermittent, religious fasting that involves no calorie restriction (CR). Ramadan fasters refrain from eating and drinking during the daytime, whereas food consumption is allowed from sunset to dawn. Although the effects of this type of fasting on the metabolism of lipids, proteins and carbohydrates remain debatable, chronobiological studies have linked Ramadan with changes in circadian distribution of body temperature, cortisol, melatonin and blood glucose levels (Roky et al 2004). Accordingly, decreased nocturnal sleep, daytime alertness and psychomotor performance have been reported among Ramadan fasters (Afifi 1997).

Alternative dietary models have been recently shown to promote human health and are gaining popularity worldwide. In this context, intermittent fasting (IF) is a nutritional pattern characterised by periodical abstinence from eating (Varady and Hellerstein 2007). Different types of IF can be found in the literature: a) time restricted eating (TRE), in which eating is allowed during a specific time-window of the day, i.e. 8 hours followed by fasting for the remaining 16 hours of the day (Tinsley and Paoli 2019). Typically, this dietary plan does not involve CR during the time period of eating. b) periodic fasting, in which fasting is practiced for up to 24 hours for specific days of the week with ad libitum (ad lib) food intake for the remaining days and c) alternate-day fasting (ADF), in which ad lib food intake and fasting days (<25% of total energy needs) alternate during the week, with some ADF protocols suggesting no food intake on fast days (Barnosky et al. 2014).

Despite the great variability in terms of forms and practices, existing studies are generally pointing towards favourable effects of IF on body composition and CV risk factors, through a variety of mechanisms (Rothschild et al. 2014). However, the clinical implications of such dietary models are still under investigation (Varady and Hellerstein 2007; Barnosky et al. 2014; Rothschild et al. 2014).

Up to now, studies investigating the effects of OF and IF on human health are limited. The aim of the present study was to comparatively evaluate the effects of two different nutritional plans on glycaemic, lipid and anthropometric profiles of overweight adults: the Athonian OF, a vegetarian advocacy of continuous energy restriction versus a hybrid model of combined CR and TRE, assessing their suitability as diets for the promotion of optimal cardiometabolic health.

Materials and methods

Study population

Participants were employees of the AHEPA University Hospital and the Aristotle University of Thessaloniki, Greece and were recruited between December 1, 2018 and February 28, 2019 via advertisements in the university and the hospital websites.

Exclusion criteria were: i) presence of chronic kidney disease, severe liver disease, prediabetes / DM or uncontrolled hypothyroidism (not adequately controlled or firstly diagnosed and receiving no treatment), ii) recent surgical operations or infections, iii) treatment with agents affecting body weight (BW), glucose metabolism and lipid profile (statins, corticosteroids, antipsychotics), iv) consumption of vitamins or mineral supplements, vi) physical disabilities and/or neurodegenerative diseases that could affect physical activity and vii) acute infections and chronic degenerative diseases.

Dietary intervention

Individuals that were regularly practicing OF for many consecutive years due to spiritual beliefs were selected to participate in the OF group and the rest of participants were assigned to the TRE group. The intervention period lasted seven weeks (48 days)

and took place during Lent fasting, preceding Orthodox Easter (March and April, 2019). Both groups followed a hypocaloric diet, providing a total of 1200-1500 kilocalories (kcal) [(5020.8-6276 kilojoules (kJ)] per day for women and 1500-1800 kcal (6276-7531.2 kJ) per day for men. Their daily energy requirements were calculated based on their daily basal metabolic rate, adjusted for an expected weight loss of ≥ 0.5 kilogram (kg) per week (energy deficit of 500-750 kcal / 2092-3138 kJ per week) and estimated according to the equations provided by the AHA recommendations for the management of overweight and obesity (Jensen et al. 2014).

TRE individuals were asked to eat from 08:00 to 16:00h daily, and fast from 16:00 to 08:00h daily. During the 8-h eating window, participants were advised to follow their given dietary plans, consisted of two meals (08:00 and 13:00h) and two snacks (11:00 and 15:30h). During the fasting period, subjects were free to consume water and energy-free beverages, such as tea, coffee, and sodas. The OF group followed a dietary plan based on the principles of Athonian fasting and abstained from consuming animal products (meat, poultry, fish, eggs, dairy and cheese), with the exception of two days during the fasting period, when fish were allowed.

The recommended amounts from each food group in OF and TRE groups were decided according to the standards of the Greek Orthodox Church fasting practice (Karras et al. 2017, 2019) and the United States (US) Department of Agriculture Dietary Guidelines (The Healthy US Style Eating Pattern) (U.S. Department of Health and Human Services and U.S. Department of Agriculture 2015) and the Greek National Dietary Guidelines for Adults (Greek National…2014), respectively. Adherence to dietary plans was evaluated with a 3-day food record (two weekdays and one weekend day), at the end of the study period. The Nutrition Analysis Software Food Processor (ESHA Research 2018) (Food Processor Analysis Software 2018) was used to analyse the 3-day food

records. Dietitians of the research team contacted all participants twice during the intervention to confirm their adherence to diets and resolve potential issues. Finally, all participants were asked to maintain a stable level of physical activity during the study period, defined as 150 minutes per week of moderate-intensity aerobic exercise, according to the AHA recommendations (Jensen et al. 2014).

Anthropometric measurements

Height was measured to the nearest 0.1 centimetre (cm) with a Holtain wall stadiometer. Waist circumference (WC) was measured midway between the lowest rib and the iliac crest by using an anthropometric tape. BW was recorded to the nearest 0.01 kg using a calibrated computerised digital balance (K-Tron P1-SR, USA Onrion IIc); each participant was barefoot and lightly dressed during measurement. The Body Mass Index (BMI) was calculated as the ratio of weight in kilograms divided by the height in meters squared (kg/m^2) (World Health Organization 2019). Body fat (BF) mass and percentage, muscle mass (MM) and lean body mass (LBM), were measured using bioelectrical impedance analysis (BIA) (SC-330 S, Tanita Corporation, Tokyo) (Tanita Academy 2019). Anthropometric evaluation was separately performed by two investigators (SK and LA).

Biochemical analysis

Blood samples were drawn in the morning, after a 12-hour overnight fast, one day before and following the end of fasting period, by ante-cubital venepuncture and samples were stored at -20°C prior to analysis. Fasting glucose (FPG), fasting insulin (FPI), serum lipid profile [total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG),

apolipoprotein A (ApoA) and apolipoprotein B-100 (ApoB-100)] and high sensitivity C-reactive protein (hs-CRP) determinations were performed using the system of automated analysers COBAS 8000 (D-68298; Roche Diagnostics, Mannheim, Germany).

Reference range of values as well as inter and intra-assay coefficients of variation for the examined parameters are as follows: FPG: 70-100 mg/dl, 1.15% and 0.53%, FPI: <25 mIU/L, 3.6% and 1.1%, TC: 100-200 mg/dl, 1.5% and 1.6%, HDL-C: >45 mg/dl, 1.46% and 1.54%, LDL-C: <130 mg/dl: optimal, 130-159 mg/dl: borderline high, 160-189 mg/dl: high, >190 mg/dl: very high, TG: <150 mg/dl: normal, 150-199 mg/dl: moderately high, 200-499 mg/dl: high, >500 mg/dl: very high, 1.85% and 0.73%, ApoA: 104-215 mg/dl, 2.5% and 1.23%, ApoB-100: 63-125 mg/dl, 2.8% and 1.6%, and hs-CRP < 0,5mg/dl, 5.25% and 1.0% (Roche Diagnostics 2019).

Insulin resistance was calculated using the homeostatic model assessment for calculating insulin resistance (HOMA-IR) as follows: FPI (μU/ml) x FPG (mmol/L)/22.5. Pancreatic beta cell function was calculated using the homeostatic model assessment of beta-cell function (HOMA-B), as follows: (20 X FPI)/ (FPG – 3.5). Both formulae are as described by Matthews et al. (1985), where FPI stands for fasting plasma insulin and FPG for fasting plasma glucose.

Statistical analysis

Kolmogorov-Smirnov analysis was carried out on the data to test for normality. Results indicated that body fat, triglyceride and energy intake did not meet parametric assumptions therefore differences between groups were calculated using Mann-Whitney U tests. All other parameters were normally distributed. Group differences at baseline and after treatment were tested using independent samples t-tests (or Mann-

Whitney test). Paired sample t-tests were used to compare between anthropometric, biochemical and dietary measurements before and after intervention within the OF and TRE groups. Mixed model ANOVA was used to assess the interaction effects of diet between the groups. For all tests a significance level of $p<0.05$ was used. Statistical analysis was carried out using SPSS version 24 (IBM, Armonk, NY, USA).

Ethical considerations

All procedures performed in the present study were in accordance with the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all individual participants included in the study. The research protocol was approved by the Ethics Committee of the AHEPA University Hospital (approval number 25224/2019).

Results

39 individuals were initially screened for inclusion in the OF group. Among them, one had a history of treatment with statins and another with metformin and therefore, were excluded. One participant opted-out during the study due to being unable to adhere to the diet. As a result, data in the OF group were available for 37 individuals (26 female / 11 male, mean age 50.11 ± 8.66 years) at baseline and for 36 persons at the end of the study period**.** The last time these regular fasters had practiced OF for a long period before their inclusion in the study, was approximately 3 months ago, during the Christmas fasting period (5 weeks); in addition, they were restraining from meat, olive oil and dairy products on every Wednesday and Friday throughout the year, according to the Orthodox Church rules.

24 persons were initially screened for inclusion in the TRE group. One was excluded due to history of antidiabetic treatment and one opted-out during the study for personal reasons. Data in the TRE group were available for 23 participants (17 female / 6 male, mean age 46.43 ± 9.2 years) at baseline and for 22 participants at the end of the intervention.

Dietary parameters

Mean daily energy intake among Orthodox fasters at baseline was 1535.5 ± 176.3 kcal (6424.5 ± 737.6 kJ) and at the end of the study was 1648.5 ± 278.3 kcal (6897.3 ± 1164.4 kJ). The dietary macronutrient distribution in this group was 45-55% [of total daily energy intake (TEI)] carbohydrates, 10-20% protein and 30-40% fat.

The dietary macronutrient distribution in the TRE group was 52-55% (of TEI) carbohydrates, 15-18% protein and 30% fat. Mean daily energy intake for the TRE group at baseline was 1579.3 ± 154.0 kcal (6607.7 ± 644.3 kJ) and at the end of the study was 1718.9 ± 285.2 kcal (7191.9 ± 1193.3 kJ), being not different from the respective energy intake of Orthodox fasters (p=0.130). **Table 1** presents the diet composition and macronutrients distribution in both groups at baseline and at the end of the study.

Body composition and anthropometric measurements

Before and after OF

At the end of the fasting period, Orthodox fasters demonstrated significant reductions in BW (75.94 ±15.74 vs 78.13 ± 16.39 kg, p<0.001), BMI (27.20 ± 5.10 vs 28.54 ± 5.45 kg/m^2, p<0.001) and WC (90.30 ± 13.91 vs 91.10 ± 13.88 cm, p=0.036), compared with pre-fasting values. No significant differences before and after the fasting were

noticed with respect to LBM (47.51 ± 9.91 vs 46.75 ± 11.03 kg, p=0.362), BF (29.32 ± 14.14 vs 28.30 ± 12.68 kg, p=0.186) and MM (48.80 ± 9.76 vs 47.94 ± 10.84 kg, p=0.212). **Table 2** presents the comparisons between features of the OF group, before and after fasting.

Before and after TRE

Following the diet, participants in the TRE group demonstrated significant reductions in BW (70.48 ± 11.73 vs 72.04 ± 12.54 kg, p=0.001), BMI (25.81 ± 3.78 vs 26.40 ± 4.11 kg/m^2, p=0.001) and WC (84.09 ± 9.57 vs 86.13 ± 10.66 cm, p=0.009), compared with their pre-diet values. No significant differences before and after the intervention were observed regarding LBM (50.54 ± 12.77 vs 49.06 ± 15.57 kg, p=0.412) and MM (48.76 ± 9.85 vs 48.49 ± 9.61 kg, p=0.330). In contrast, BF mass was significantly lower after the diet (22.01 ± 7.32 vs 23.05 ± 7.61 kg, p=0.001). **Table 3** presents the comparisons between features of the TRE group, before and after the diet.

Interactions

At baseline, Orthodox fasters and the TRE group presented comparable BW (78.13 ± 16.39 vs 72.04 ± 12.54 kg, p=0.120), BMI (28.54 ± 5.45 vs 26.40 ± 4.11 kg/m^2, p=0.098), WC (91.10 ± 13.88 vs 86.13 ± 10.66 cm, p=0.143), LBM (47.51 ± 9.91 vs 50.54 ± 12.77 kg, p=0.341), BF (29.32 ± 14.14 vs 23.05 ± 7.61 kg, p=0.132) and MM (48.80 ± 9.76 vs 48.76 ± 9.85 kg, p=0.989) values. **Table 4** presents the comparisons between baseline features of the two groups.

Following the dietary intervention, Orthodox fasters and the TRE group did not differ with respect to BW (75.94 ± 15.74 vs 70.48 ± 11.73 kg, p=0.159), BMI (27.20 ± 5.10 vs 25.81 ± 3.78 kg/m^2, p=0.110), LBM (46.75 ± 11.08 vs 49.06 ± 15.57 kg, p=0.301),

BF (28.30 ± 12.68 vs 22.01 ± 7.32 kg, p=0.150) and MM (47.94 ± 10.84 vs 48.49 ± 9.61 kg, p=0.848) values. In contrast, the TRE group presented lower WC values (84.09 ± 9.57 vs 90.30 ± 13.91 cm, p=0.049) than the OF group. **Table 5** presents the comparisons between features of the two groups, following the intervention.

Blood parameters

Before and after OF

Participants in the OF group manifested lower TC (178.40 ± 34.14 vs 197.17 ± 34.30 mg/dl, p<0.001), HDL-C (51.01 ± 11.66 vs 53.91 ± 12.31 mg/dl, p=0.009) and LDL-C (105.89 ± 28.08 vs 122.37 ± 29.70 mg/dl, p<0.001) concentrations after the diet, compared with their pre-diet values. In contrast, ApoA and ApoB-100 concentrations did not present significant differences before and after the fasting (146.79 ± 23.70 vs 142.56 ± 23.42 mg/dl, p=0.133 and 98.44 ± 27.01 vs 96.73 ± 26.60 mg/dl, p=0.554, respectively). FPG (84.23 ± 7.96 vs 85.17 ± 9.53 mg/dl, p=0.554), FPI (10.08 ± 7.46 vs 9.98 ± 9.00 μIU/ml, p=0.927), HOMA-B (193.01 ± 134.43 vs 168.36 ± 124.11, p=0.293), HOMA-IR (2.14 ± 1.69 vs 2.12 ± 1.98, p=0.923) and hs-CRP (0.24 ± 0.25 vs 0.23 ± 0.54 mg/dl, p=0.885) values did not present significant changes before and following the fasting **(Table 2)**.

Before and after TRE

In the TRE group, TC (201.26 ± 28.41 vs 197.09 ± 29.61 mg/dl, p=0.286), ApoA (164.91 ± 28.09 vs 158.52 ± 26.85 mg/dl, p=0.140) and ApoB-100 (107.00 ± 20.43 vs 107.26 ± 22.24 mg/dl, p=0.902) concentrations remained unchanged before and after the diet. In contrast, participants manifested higher TG (90.26 ± 26.78 vs 81.71 ± 29.07 mg/dl, p=0.036) and lower HDL-C concentrations (60.13 ± 15.93 vs 64.04 ± 16.72

mg/dl, p=0.023) at the end of the intervention, compared with their baseline values. FPG (87.48 ± 9.96 vs 83.52 ± 8.94 mg/dl, p=0.087), FPI (11.33 ± 16.01 vs 8.08 ± 4.88 μIU/ml, p=0.344), HOMA-B (126.22 ± 58.64 vs 163.72 ± 104.59, p=0.059), HOMA-IR (1.80 ± 1.11 vs 1.72 ± 1.15, p=0.781) and hs-CRP (0.12 ± 0.11 vs 0.20 ± 0.25 mg/dl, p=0.077) values did not present significant changes before and following the fasting (**Table 3)**.

Interactions

At baseline, TC (197.17 ± 34.30 vs 201.26 ± 28.41 mg/dl, p=0.548), LDL-C (122.37 ± 29.70 vs 120.87 ± 28.74 mg/dl, p=0.945) and ApoB-100 (98.44 ± 27.01 vs 107.00 ± 20.43 mg/dl, p=0.219) concentrations did not differ significantly between the OF and the TRE group. In contrast, the OF group manifested higher TG (102.80 ± 45.54 vs 81.71 ± 29.07 mg/dl, p=0.026) and lower HDL-C (53.91 ± 12.31 vs 64.04 ± 16.72 mg/dl, p=0.008) and ApoA (146.79 ± 23.70 vs 164.91 ± 28.09 mg/dl, p=0.008) concentrations, compared with the TRE subjects. FPG (84.23 ± 7.96 vs 87.48 ± 9.96 mg/dl, p=0.221), FPI (10.08 ± 7.46 vs 11.33 ± 16.01 μIU/ml, p=0.909), HOMA-IR (2.14 ± 1.69 vs 1.80 ± 1.11, p=0.209) and hs-CRP (0.24 ± 0.25 vs 0.12 ± 0.11 mg/dl, p=0.075) values did not significantly differ between the OF and the TRE group. The HOMA-B index was lower in the TRE than the OF group (126.22 ± 58.64 vs 193.01 ± 134.43, p=0.022) (**Table 4)**.

Following the intervention, Orthodox fasters had lower TC (178.40 ± 34.14 vs 197.09 ± 29.61 mg/dl, p=0.028), HDL-C (51.01 ± 11.66 vs 60.13 ± 15.93 mg/dl, p=0.013) and ApoA (142.56 ± 23.42 vs 158.52 ± 26.85 mg/dl, p=0.019) levels, compared with TRE participants. ApoB-100 concentrations were comparable between the groups (96.73 ± 26.60 vs 107.26 ± 22.24 mg/dl, p=0.106). FPG (85.17 ± 9.53 vs 83.52 ± 8.94 mg/dl,

p=0.576), FPI (9.98 ± 9.00 vs 8.08 ± 4.88 μIU/ml, p=0.378), HOMA-B (168.36 ± 124.11 vs 163.72 ± 104.59, p=0.854), HOMA-IR (2.12 ± 1.98 vs 1.72 ± 1.15, p=0.415) and hs-CRP (0.23 ± 0.54 vs 0.20 ± 0.25 mg/dl, p=0.835) values did not significantly differ between the OF and the TRE group (**Table 5)**.

Discussion

To the best of our knowledge, this is the first study comparatively assessing the effects of OF and a different dietary pattern on anthropometric, lipid and glycaemic profiles. In addition, ApoA and ApoB-100 concentrations were determined for the first time in the present study in a population of Orthodox fasters, before and following the fasting. Its originality also lies on the fact that in one of the study groups, TRE and CR were combined in the same nutritional plan. The results showed that both OF and the TRE diet resulted in improvements in the anthropometric features of the participants, with OF also presenting lipid-lowering effects.

Previously published clinical studies (Sarri et al. 2003; Karras et al. 2017, 2019) and systematic reviews (Koufakis et al. 2017) have highlighted the optimal effects of OF on blood lipids and more specifically on TC and LDL-C concentrations, which have been shown to decline up to 17.8 and 31.4 % respectively, during the fasting periods (Koufakis et al. 2018). Potential mechanisms mediating these effects are the decreased consumption of SFA, leading to increased number of LDL receptors (Mustad et al. 1997) and the restriction in energy intake (Koufakis et al. 2018). Similar to other vegetarian diets, OF results in a parallel decrease of HDL-C and ApoA concentrations. It is well established that HDL-C levels present an adverse association with CV risk and that this relationship remains significant even for individuals with very low LDL-C concentrations (< 70 mg/dl), as those treated with statins (Barter et al. 2007). In a

similar way, ApoA levels have been shown to predict recurrent CV events and all-cause mortality in secondary prevention studies, suggesting that this biomarker might be useful for CV risk estimation in people with CAD (Van Lennep et al. 2000). Accumulating evidence suggests that ApoB-100 might be a superior to LDL-C marker for assessment of CV risk and its addition to the routine lipid panel to enhance patient management has been proposed (Contois et al. 2009). In our study, ApoB-100 levels were not found to be affected by the two diets; however, previous reports have proved a significant reduction in its concentrations, following a consumption of a defined, plant-based diet for 4 weeks (Najjar et al. 2018), as well as during Ramadan fasting (Adlouni et al. 1998).

TG concentrations have been previously shown to increase during fasting (Sarri et al. 2003; Koufakis et al. 2017, 2018), probably because of increased carbohydrate intake (carbohydrate-induced hypertriglyceridemia) (Hudgins 2000). The exact impact of the aforementioned lipid changes on vegetarians' health remains controversial. A recently published, large observational study which followed 48188 participants for 18 years, showed that fish eaters and vegetarians had lower rates of CAD than meat eaters, although vegetarians had higher rates of haemorrhagic and total stroke (Tong et al. 2019).

Studies in the field of IF are characterised by significant heterogeneity in terms of included population, type of dietary intervention and explored outcomes. However, recent works conducted on both animals and humans, have associated IF with optimal metabolic outcomes, mediated by changes in hormonal environment, including an increase in plasma concentrations of adiponectin and a decrease in leptin and resistin levels, optimisation of circadian rhythms and gut microbiome (Melkani and Panda 2017). Several studies have proved optimal effects of IF plans on BW and composition.

A systematic review and meta-analysis of eleven trials demonstrated that intermittent energy restriction was not inferior to the continuous approach, in terms of weight loss (− 0.61 kg, 95% CI − 1.70 to 0.47; p = 0.27) (Cioffi et al. 2018). Worth noting, the metabolic benefits of IF are not exclusively dependent on reduction in BW. As shown in a proof-of-concept study by Sutton et al. (2018), 5 weeks of early TRE (6-hr eating period, with dinner before 3 p.m.) improved beta-cell responsiveness, insulin sensitivity, blood pressure, oxidative stress, and appetite, irrespectively of weight loss in people with prediabetes.

Similar to our observations, Gabel et al. (2018), did not prove a significant reduction in plasma lipids and glycaemic parameters in obese adults, following an 8-h TRE plan for 12 weeks, despite an achieved weight loss of approximately 2.6%. Moro et al. (2016), investigated the impact of a 16/8 TRE pattern on body composition, inflammation and CV risk factors in resistance-trained individuals. Although a decrease in fat mass was observed in the TRE compared with the control group (p=0.04), no significant differences in lipid profile, insulin and glucose levels were shown between the two groups. However, adiponectin concentrations were higher and Tumour Necrosis Factor-α and interleukin-1β levels were lower in TRE subjects than controls, at the end of the 8-week intervention.

Orthodox fasters have been previously reported to present higher pre-fasting serum concentrations of the antioxidant factors retinol and a-tocopherol than non-fasting controls (Sarri et al. 2009). Our results failed to establish a significant impact of any of the two diets on systematic inflammation and glycaemic parameters. Yet, it should be noted that the present study included subjects with overweight, otherwise metabolically healthy, with normal baseline levels of hs-CRP, glucose and insulin. As a result,

significant changes of the aforementioned parameters in such a population and in a relatively short time period are difficult to be demonstrated.

Our study presents several limitations. The small sample size and the short time period of the intervention, might have attenuated its power to reveal changes in the parameters investigated. Ideally, participants should have been randomised in the two arms. However, the adoption of religious fasting is closely related to the religious beliefs of each person and randomisation could not have been performed without violating these beliefs. The impact of physical activity on study results should be considered; yet, the fact that participants were asked to maintain a standard level of physical activity during the study might - in part – have counteracted the confounding effects of this parameter. Albeit hs-CRP levels contribute valuable information with respect to CV risk and mortality (Yousuf et al. 2013), the evaluation of alternative inflammation markers, such as serum adipokines and cytokines, would further enhance the validity of our results. Moreover, the method (BIA) used for body composition assessment was not the gold standard, since the measurements can be confounded by clinical status, such as the presence of oedema (Wells and Fewtrell, 2006).

The OF group presented higher TG and lower HDL-C and ApoA concentrations than the TRE group at baseline. This is not unexpected, given that participants in the OF group have been following this dietary plan with great adherence for many consecutive years, for religious and spiritual reasons. Plant-based dietary patterns generally have a lipid-lowering effect that was evident among Orthodox fasters included in this study. On the other hand, it is also well established that the OF impact on lipids is not sustainable after the fasting cessation; an increase in TC and LDL-C levels, up to 6% and 9% respectively, has been observed when fasters return to their standard dietary habits (Koufakis et al. 2018). Finally, self-report dietary assessment data, although

widely used in clinical nutrition research, might be challenged for accuracy (Archer et al. 2018). It should be noted however, that – at least for the OF group- this parameter might have a minimal impact on our results, since adherence to this dietary pattern is determined by long-standing religious beliefs of the participants.

Conclusion

In conclusion, the results of this small, pilot study suggest that OF and a hybrid model of CR and TRE exert comparable effects on BW. However, OF results in greater reductions of TC and atherogenic LDL-C concentrations than the TRE plan. The exact mechanisms mediating the impact of both diets on human health, are yet to be determined. Studies involving larger sample sizes and with longer follow-up periods are needed to replicate the findings of the present study.

Author contributions

SNK conceptualised and designed the study. SNK, TK, LA and VA collected all data. LA designed the dietary intervention. PK, KT and KM conducted the biochemical analysis of the samples. EM and AP performed the statistical analysis. SNK, TK, HM, PZ and KK analyzed and interpreted the dietary data and the biochemical results. SNK and TK performed the literature review and drafted the first version of the manuscript. All authors have read and critically revised the manuscript and approved the final version.

Acknowledgements: None

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of interest: None

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Table 1: Diet composition and macronutrients distribution at baseline and at the end of the study in both groups

	Baseline				End of study			
	OF (n=37)		TRE (n=23)		OF (n=36)		TRE (n=22)	
	M	SD	M	SD	M	SD	M	SD
Energy (kcal/day)	1535.5	176.3	1579.3	154.0	1648.5	278.3	1718.9	285.2
Carbohydrates (kcal/day)	778.3	95.6	846.3	80.7	840.8	142.8	889.9	146.7
Protein (kcal/day)	228.1	58.5	266.0	44.8	227.2	68.9	312.1	61.8
Fat (kcal/day)	529.6	59.2	467.0	39.4	578.6	95.6	518.9	96.2
% Carbohydrates	50.7	2.6	53.6	1.3	51.0	2.7	51.8	2.4
% Protein	14.7	2.5	16.8	1.8	13.6	2.0	18.2	1.9
% Fat	34.6	2.7	29.6	0.7	35.2	2.8	30.1	1.3
% Saturated fat	< 10	-	< 10	-	< 10	-	< 10	-

Values are presented as mean (M) ± standard deviation (SD).

Abbreviations: kcal: kilocalories; OF: Orthodox fasting; TRE: Time restricted eating

Table 2: Comparisons between features of Orthodox fasters before and after the fasting

	Orthodox Fasters						
	Before (n=37)		**After (n=36)**				
	M	SD	M	SD	p-value	t	d
Weight (kg)	78.13	16.39	75.94	15.74	**<.001**	7.05	1.168
BMI (kg/m^2)	28.54	5.45	27.20	5.10	**<.001**	7.12	1.873
Body Fat (%)	34.44	9.15	34.25	8.79	.844	.198	.033
Body Fat (kg)	29.32	14.14	28.30	12.68	.186	1.42	.427
Lean Body Mass (kg)	47.51	9.91	46.75	11.03	.362	1.23	.445
Muscle Mass (kg)	48.80	9.76	47.94	10.84	.212	1.27	.212
WC (cm)	91.10	13.88	90.30	13.91	**.036**	2.19	.372
Hs-CRP (mg/dl)	.24	.25	.23	.54	.885	.15	.017
Fasting glucose (mg/dl)	84.23	7.96	85.17	9.53	.554	-.60	.101
TC (mg/dl)	197.17	34.30	178.40	34.14	**<.001**	6.10	1.033
TG (mg/dl)	102.80	45.54	108.59	74.63	.549	-.61	.102
HDL-C (mg/dl)	53.91	12.31	51.01	11.66	**.009**	2.78	.470
LDL-C (mg/dl)	122.37	29.70	105.89	28.08	**<.001**	5.98	1.010
Apolipoprotein A (mg/dl)	146.79	23.70	142.56	23.42	.133	1.54	.264
Apolipoprotein B (mg/dl)	98.44	27.01	96.73	26.60	.554	.60	.103
Fasting Insulin (μIU/ml)	10.08	7.46	9.98	9.00	.927	.09	.016
HOMA-B	193.01	134.43	168.36	124.11	.293	1.07	.183
HOMA-IR	2.14	1.69	2.12	1.98	.923	.097	.015

Values are presented as mean (M) ± standard deviation (SD). Significant differences are presented in bold.

Abbreviations: BMI: Body Mass Index; WC: Waist Circumference; Hs-CRP: High-sensitivity C-Reactive protein; TC: Total Cholesterol; TG: Triglycerides; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol; HOMA-B: homeostatic model assessment for beta-cell function; HOMA-IR: homeostatic model assessment for insulin resistance

Table 3: Comparisons between features of the TRE group before and after the diet

	TRE group						
	Before (n=23)		After (n=22)				
	M	SD	M	SD	p-value	t	d
Weight (kg)	72.04	12.54	70.48	11.73	**.001**	3.70	.762
BMI (kg/m^2)	26.40	4.11	25.81	3.78	**.001**	3.83	.800
Body Fat (%)	31.92	8.51	30.63	8.27	.055	2.03	.425
Body Fat (kg)	23.05	7.61	22.01	7.32	**.001**	3.93	.811
Lean Body Mass (kg)	50.54	12.77	49.06	15.57	.412	.897	.321
Muscle Mass (kg)	48.76	9.85	48.49	9.61	.330	.995	.203
WC (cm)	86.13	10.66	84.09	9.57	**.009**	2.85	.594
Hs-CRP (mg/dl)	.12	.11	.20	.25	.077	-1.87	.372
Fasting glucose (mg/dl)	87.48	9.96	83.52	8.94	.087	1.79	.374
TC (mg/dl)	201.26	28.41	197.09	29.61	.286	1.09	.228
TG (mg/dl)	81.71	29.07	90.26	26.78	**.036**	-2.24	.467
HDL-C (mg/dl)	64.04	16.72	60.13	15.93	**.023**	2.45	.510
LDL-C (mg/dl)	120.87	28.74	118.87	26.84	.511	.67	.139
Apolipoprotein A (mg/dl)	164.91	28.09	158.52	26.85	.140	1.53	.319
Apolipoprotein B (mg/dl)	107.00	20.43	107.26	22.24	.902	-.13	.026
Fasting Insulin (μIU/ml)	11.33	16.01	8.08	4.88	.344	.97	.207
HOMA-B	126.22	58.64	163.72	104.59	.059	-1.99	.541
HOMA-IR	1.80	1.11	1.72	1.15	.781	.281	058

Values are presented as mean (M) ± standard deviation (SD). Significant differences are presented in bold.

Abbreviations: BMI: Body Mass Index; WC: Waist Circumference; Hs-CRP: High-sensitivity C-Reactive protein; TC: Total Cholesterol; TG: Triglycerides; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol; HOMA-B: homeostatic model assessment for beta-cell function; HOMA-IR: homeostatic model assessment for insulin resistance; TRE: Time restricted eating

Table 4: Comparisons between baseline features of the two groups

	Group						
	OF (n=37)		**TRE (n=23)**				
	M	SD	M	SD	p-value	t	d
Age (years)	50.11	8.66	46.43	9.2	0.128	-	-
Height (m)	1.65	.09	1.65	.09	0.799	-	-
Weight (kg)	78.13	16.39	72.04	12.54	.120	1.56	.4142
BMI (kg/m^2)	28.54	5.45	26.40	4.11	.098	1.68	.4461
Body Fat (%)	34.44	9.15	31.92	8.51	.247	1.17	.3107
Body Fat (kg)	29.32	14.14	23.05	7.61	.132	1.60	.5698
Lean Body Mass (kg)	47.51	9.91	50.54	12.77	.341	1.32	.4567
Muscle Mass (kg)	48.80	9.76	48.76	9.85	.989	-.014	.0037
WC (cm)	91.10	13.88	86.13	10.66	.143	1.49	.3977
Hs-CRP (mg/dl)	.24	.25	.12	.11	.075	1.81	.4898
Fasting glucose (mg/dl)	84.23	7.96	87.48	9.96	.221	-1.24	-.331
TC (mg/dl)	197.17	34.30	201.26	28.41	.548	-.60	-.1602
TG (mg/dl)	102.80	45.54	81.71	29.07	**.026**	2.28	.5953
HDL-C (mg/dl)	53.91	12.31	64.04	16.72	**.008**	-2.77	-.7394
LDL-C (mg/dl)	122.37	29.70	120.87	28.74	.945	.07	.0187
Apolipoprotein A(mg/dl)	146.79	23.70	164.91	28.09	**.008**	-2.77	-.7394
Apolipoprotein B (mg/dl)	98.44	27.01	107.00	20.43	.219	-1.243	-.3318
Fasting Insulin (μIU/ml)	10.08	7.46	11.33	16.01	.909	-.114	-.0304
HOMA-B	193.01	134.43	126.22	58.64	**.022**	2.36	.63
HOMA-IR	2.14	1.69	1.80	1.11	.209	1.27	.339

Values are presented as mean (M) ± standard deviation (SD). Significant differences are presented in bold.
Abbreviations: BMI: Body Mass Index; WC: Waist Circumference; Hs-CRP: High-sensitivity C-Reactive protein; TC: Total Cholesterol; TG: Triglycerides; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol; HOMA-B: homeostatic model assessment for beta-cell function; HOMA-IR: homeostatic model assessment for insulin resistance; OF: Orthodox fasting; TRE: Time restricted eating

Table 5: Comparisons between features of the two groups after the diet

	Group						
	OF (n=36)		TRE (n=22)				
	M	SD	M	SD	p-value	t	d
Weight (kg)	75.94	15.74	70.48	11.73	.159	1.43	.3817
BMI (kg/m^2)	27.20	5.10	25.81	3.78	.110	1.62	.4324
Body Fat (%)	34.25	8.79	30.63	8.27	.120	1.58	.4218
Body Fat (kg)	28.30	12.68	22.01	7.32	.150	1.53	.5609
Lean Body Mass (kg)	46.75	11.08	49.06	15.57	.301	1.44	.4765
Muscle Mass (kg)	47.94	10.84	48.49	9.61	.848	-.193	-.051
WC (cm)	90.30	13.91	84.09	9.57	**.049**	2.01	.5395
Hs-CRP (mg/dl)	.23	.54	.20	.25	.835	.21	.0571
Fasting glucose (mg/dl)	85.17	9.53	83.52	8.94	.576	.56	.1496
TC (mg/dl)	178.40	34.14	197.09	29.61	**.028**	-2.25	-.601
TG (mg/dl)	108.59	74.63	90.26	26.78	.248	1.17	.3123
HDL-C (mg/dl)	51.01	11.66	60.13	15.93	**.013**	-2.57	-.686
LDL-C (mg/dl)	105.89	28.08	118.87	26.84	.067	-1.87	-.499
Apolipoprotein A (mg/dl)	142.56	23.42	158.52	26.85	**.019**	-2.42	-.650
Apolipoprotein B (mg/dl)	96.73	26.60	107.26	22.24	.106	-1.64	-.440
Fasting Insulin (μIU/ml)	9.98	9.00	8.08	4.88	.378	.889	.2419
HOMA-B	168.36	124.11	163.72	104.59	.854	.185	.0501
HOMA-IR	2.12	1.98	1.72	1.15	.415	.821	.2234

Values are presented as mean (M) ± standard deviation (SD). Significant differences are presented in bold.

Abbreviations: BMI: Body Mass Index; WC: Waist Circumference; Hs-CRP: High-sensitivity C-Reactive protein; TC: Total Cholesterol; TG: Triglycerides; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol; HOMA-B: homeostatic model assessment for beta-cell function; HOMA-IR: homeostatic model assessment for insulin resistance; OF: Orthodox fasting; TRE: Time restricted eating