Martínez-Montoro *et al. BMC Medicine* (2025) 23:368
https://doi.org/10.1186/s12916-025-04182-z

BMC Medicine

RESEARCH

Open Access

Effect of a ketogenic diet, time-restricted eating, or alternate-day fasting on weight loss in adults with obesity: a randomized clinical trial

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Abstract

Background Studies evaluating the effects of novel, alternative dietary approaches for weight loss compared with the Mediterranean diet (MedDiet) are lacking. We aimed to evaluate the effects of diets with varying ketogenic potential, i.e., a very-low carbohydrate diet (ketogenic diet, KD), time-restricted eating (TRE), and modified alternate-day fasting (mADF) on weight loss in obesity, compared with a MedDiet.

Methods Three-month, parallel-arm, randomized clinical trial including 160 adults with obesity. Participants were randomized to 1 of 5 groups: control (MedDiet), KD, early TRE (eTRE), late TRE (lTRE), or mADF. All diets were calorie-restricted. The primary outcome was differences in weight loss from baseline to 3 months between a calorie-restricted MedDiet and each of the four remaining calorie-restricted dietary interventions. Secondary outcomes included change in body mass index, body composition, and cardiometabolic risk factors.

Results The mean age was 45.7 years (SD 10.7), and 70.6% were women. One hundred forty participants completed the study. Significant differences in weight loss from baseline to 3 months were found between KD and the control group [−3.78 kg (−5.65 to −1.91 kg)], between mADF and the control group [−3.14 kg (−4.98 to −1.30 kg)], and between lTRE and the control group [−2.27 kg (−4.13 to −0.40 kg)], but not between eTRE and the control group [−1.22 kg (−3.07 to 0.64 kg)].

Conclusions These results suggest that a calorie-restricted KD, mADF, or lTRE may be more effective for weight loss than a calorie-restricted MedDiet in obesity. Further research is needed to evaluate the long-term feasibility and efficacy of these dietary interventions compared with the MedDiet.

Trial registration ClinicalTrials.gov (NCT04453150).

Keywords Ketogenic diet, Time-restricted eating, Alternate-day fasting, Mediterranean diet, Weight loss

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Background

The prevalence of overweight and obesity is increasing globally, having nearly tripled in the last few decades, and reaching epidemic dimensions worldwide [1]. Of note, it is projected that by 2030–2035 approximately 50% of the global population will have overweight or obesity [2–4]. Excessive body weight is associated with several cardiometabolic, musculoskeletal, or psychological comorbidities, and with certain types of cancer [5]. Therefore, major health, social, and economic burdens are related to this disease [5, 6].

Different strategies are available for the treatment of obesity. It should be noted that nutritional therapy, including calorie-restricted dietary patterns, is currently the mainstay of treatment of obesity [7]. Among these dietary patterns, a large body of evidence supports that the Mediterranean diet (MedDiet), a primarily plant-based, high-unsaturated fat diet, leads to weight loss when it is energy-restricted, and has also important cardiovascular benefits in people living with obesity [8, 9]. Accordingly, this dietary pattern has been recommended by clinical guidelines for the management of obesity [7]. However, additional dietary approaches beyond traditional recommendations are needed for the treatment of this disease.

In this regard, low-carbohydrate diets, which are able to induce ketone body production, result in significant weight loss, as demonstrated in previous studies [10, 11]. On the other hand, other ketone-producing diets, such as time-restricted eating (TRE) or alternate-day fasting (ADF) may also play an important role in the treatment of obesity. TRE involves the consumption of meals within a shortened time window during the day, and emerging evidence suggests that this approach may be effective in achieving significant weight loss [12–15]. Modified ADF (mADF), a modality of intermittent fasting that alternates "fast days," in which individuals consume approximately 25–30% of total daily intake, and "feast days," with ad libitum energy intake, has also shown promising results in terms of weight loss [16, 17]. Previously, no differences in weight loss were found between a low-carbohydrate diet without calorie restriction and a calorie-restricted MedDiet in patients with obesity [11]. On the other hand, in a 16-week trial performed in patients with overweight/obesity and type 2 diabetes, a low-carbohydrate diet resulted in greater weight loss than a MedDiet (both diets were calorie-restricted) [18]. However, evidence is still limited, and there are scarce data regarding the potential effects of these diets on weight loss as compared with a calorie-restricted MedDiet, the most recommended diet for the treatment of overweight/obesity in the Mediterranean countries.

Therefore, in this study, we evaluated the effects of a very-low-carbohydrate diet (ketogenic diet, KD), TRE, or mADF (all of them calorie-restricted) on weight loss, compared with a calorie-restricted MedDiet, and we also assessed their effects on body composition and cardiometabolic risk factors.

Methods

Trial design

This was a 3-month prospective, parallel-group, randomized clinical trial conducted at the Department of Endocrinology and Nutrition, Virgen de la Victoria University Hospital (Malaga, Spain). Participants were randomly assigned in a 1:1:1:1:1 ratio to MedDiet (control group), KD, early time-restricted eating (eTRE), late time-restricted eating (lTRE), or mADF. Assessments were done at baseline, 1 month, 2 months, and 3 months (end of intervention). This study was approved by the Ethics Research Committee of Malaga (ID 1/2019-P14) and was conducted according to the principles of the Declaration of Helsinki. This trial was registered at ClinicalTrials.gov (NCT04453150). All participants gave their signed informed consent to participate in this study.

Trial participants

Participants were recruited at outpatient clinics of the Department of Endocrinology and Nutrition, Virgen de la Victoria University Hospital in Malaga. Potential candidates were identified during routine clinical visits and provided with basic information about the trial by the clinical endocrinologists of the department, and those who expressed interest were referred to further evaluation. Inclusion criteria were age between 18 and 65 years, and body mass index (BMI, calculated by weight in kilograms divided by the square of the height in meters) between 30 and 45 kg/m^2. Exclusion criteria were diabetes mellitus, current/planned pregnancy or breastfeeding, history of eating disorders, use of medication that could affect weight, unstable weight (changes > 5% in the last 3 months), history of major cardiovascular events 6 months prior to the inclusion, active cancer, acute inflammatory/infectious disease, liver dysfunction, chronic kidney disease, use of probiotics/prebiotics/antibiotics, and alcohol consumption (> 30 g/day for men; > 20 g/day for women).

Randomization and masking

Participants were randomly assigned in a 1:1:1:1:1 ratio to MedDiet KD, eTRE, lTRE, or mADF. Randomization was done by an independent statistician using a computer-generated random allocation sequence, performing a block randomization with a block size of 5 to ensure balanced group sizes throughout the trial. The allocation sequence was concealed by using sealed, opaque envelopes that were consecutively numbered and opened only at the time of assigning participants to their respective groups. Participants and investigators were not blinded. Statisticians were blinded to group allocation during data analysis.

Interventions

All participants received dietary counselling by expert nutritionists and written support materials and menus with the specific dietary plan to adhere during the intervention (including detailed daily meals, specifying food portions) at baseline visit. Standard meals were designed to provide 1800 kcal/day for men and 1400 kcal/day for women. These meals were thereafter personalized to achieve an energy deficit of 600 kcal/day based on the estimated energy requirements calculated by the Harris-Benedict formula [19].

Participants in the control group followed a calorie-restricted MedDiet (45% of calories from carbohydrates, 20% from protein, and 35% from fat, with an energy deficit of 600 kcal/day, 3 main meals distributed over 24 h: breakfast, lunch, and dinner), and were instructed to consume a primarily plant-based diet (fruits, vegetables, legumes, nuts, whole grains), olive oil as the primary source of fat, moderate consumption of fish, seafood, poultry, eggs, and a low consumption of red and processed meats. The calorie-restricted KD intervention consisted of a very-low-carbohydrate, high-fat diet (5% of calories from carbohydrates, 30% from protein, and 65% from fat, with an energy deficit of 600 kcal/day, 3 meals distributed over 24 h: breakfast, lunch, and dinner). This intervention was performed without schedule restrictions and supported by commercial replacement meals only for the first meal (100 kcal, 15 g of protein, 3 g of fat, of which 1 g was saturated fat, and 50 mg of docosahexaenoic acid, 2 g of carbohydrates, of which < 1 g was simple sugars). The calorie-restricted eTRE intervention was characterized by an 8-h eating window between 8 a.m. and 4 p.m. where participants were instructed to consume food over 3 meals (breakfast, snack, and lunch, 45% of calories from carbohydrates, 20% from protein, and 35% from fat, with an energy deficit of 600 kcal/day). The calorie-restricted lTRE presented an 8-h eating window between 2 p.m. and 10 p.m. (lunch, snack, and dinner, 45% of calories from carbohydrates, 20% from protein, and 35% from fat, with an energy deficit of 600 kcal/day). The intake of water and no-calorie beverages (e.g., tea or coffee) was allowed during the fasting periods. Finally, the mADF intervention alternated between 24 h of normocaloric intake (45% of calories from carbohydrates, 20% from protein, and 35% from fat, 3 meals distributed over 24 h: breakfast, lunch, and dinner; 4 days per week) and a modified 24-h fast (25–30% of total energy requirements, 400–800 kcal/day, 3 days per week), the latter provided by commercial replacement meals (5% of calories from carbohydrates, 30% from protein, and 65% from fat, 3 replacement meals distributed over 24 h: breakfast, lunch, and dinner). To ensure mADF was isocaloric with the other diets, a slight increase in caloric intake on non-fasting days was made when necessary. Ketonemia levels were assessed during the trial in all the study groups.

Outcomes and follow-up

This was a single-center trial conducted at the Department of Endocrinology and Nutrition, Virgen de la Victoria University Hospital (Malaga, Spain). The trial's main objective was to evaluate the impact of different calorie-restricted, ketone body-increasing diets on the gut microbiome and weight in patients with obesity, compared with a calorie-restricted MedDiet. The primary endpoint of the trial was change from baseline to 3 months in gut microbiota composition following 4 different calorie-restricted dietary interventions (including KD, eTRE, lTRE, and mADF), compared with a calorie-restricted MedDiet. The current study represents the first prospective assessment of the trial and aimed to evaluate differences in weight loss from baseline to 3 months between a calorie-restricted MedDiet and each of these 4 cal-restricted dietary interventions with varying ketogenic potential—KD, eTRE, lTRE, and mADF (primary outcome of this analysis). Additionally, we evaluated changes in BMI, body composition, and cardiometabolic risk factors from baseline to 3 months between the interventions and the control group—MedDiet (secondary outcomes of this analysis).

Three face-to-face visits (at 1, 2, and 3 months) were scheduled. Three phone visits (between baseline and the first month, the first and second month, and the second and third month, where the nutritionists checked diet plans and solved doubts) were also scheduled. Besides, participants were offered to contact the nutritionists for doubts or incidences through an instant message app during the study. Baseline measurements were conducted before randomization. Clinical and anthropometric data were collected at baseline and 1, 2, and 3 months following the intervention. Weight, height, and blood pressure measurements with standard methods were included among these data. Body composition was assessed by bioelectrical impedance analysis with a Tanita body composition analyzer (TANITA, IL, USA).

Biochemical data were collected at baseline and 3 months. Blood samples were collected following a 12-h fast. Serum was separated and immediately frozen at − 80°C. Serum glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were measured through standard laboratory enzymatic methods and following validated protocols. Low-density lipoprotein (LDL) cholesterol was calculated by the Friedewald formula [20]. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated by the formula fasting insulin (μIU/mL) × fasting glucose (mmol/L)/22.5 [21]. HbA1c was measured by chromatographic methods. To monitor all dietary interventions, ketonemia levels were evaluated by capillary testing weekly, using the Glucomen Areo B-ketone Sensor test strips (A. Menarini Diagnostics, B08PFRTXZX) and the Glucomen Areo GK glucometer (A. Menarini Diagnostics, B00QVWZL50), in a fasting state. To homogenize the number of fasting hours and take measurements at the end of the fasting window, capillary ketonemia was measured between 8 and 9 a.m. in the eTRE group, whereas it was measured between 1 and 2 p.m. in the lTRE group.

Adverse events were assessed at each visit by clinical interview and checked through medical records by the study investigators.

Statistical analysis

For the sample size calculation, we estimated that the control group (Mediterranean diet) and the other intervention groups inducing ketosis would lose 4.5 kg and 7 kg of body weight, respectively (based on own previous preliminary results) and a variance of 9 kg. We calculated that 24 participants per group would provide 80% power to detect a statistically significant difference in body weight between the intervention and control groups at 3 months, also at a 95% confidence level (1-alpha). We expected a drop-out rate of 20%. We therefore aimed to recruit at least 150 participants (30 per group).

All statistical analyses were performed using Stata 18.0 (StataCorp), and data were evaluated using intention-to-treat analyses. Continuous variables were described by means and standard deviations (SD) or means (95% confidence intervals), and categorical variables were summarized by percentages, unless otherwise indicated.

We used linear mixed models with a random intercept and an unstructured covariance matrix to compare each of the primary and secondary outcome measures across the time points between groups, and for longitudinal changes in weight and body composition within each group. The parameters were estimated by the Restricted Maximum Likelihood (REML) method. Each primary/secondary outcome was considered as a dependent variable. As independent variables, we included time points (dummies with initial time as reference category), age (in years), sex (indicator), and baseline outcome measure to control for and assess changes in dependent variables across time points. Following an established methodology described in Twisk et al. [22], we analyzed the interaction between time points and interventional group (dummies with control diet as reference group). All statistical analyses were two-sided, and a p value < 0.05 was considered statistically significant.

Results

Characteristics of the study population

From January 2020 to March 2022, 160 participants were randomly assigned to 1 of 5 groups: control group, (n=32), KD (n=32), eTRE (n=32), lTRE (n=32), or mADF (n=32). A total of 140 participants (87.5%) completed the 3-month intervention. One hundred sixty and 151 participants completed the first and second months of the intervention, respectively. The flowchart of the study participants is shown in Fig. 1. Clinical characteristics of the study population at baseline are shown in Table 1. Mean age (± SD) was 45.7 ± 10.7 years, and mean weight was 107.5 ± 19.5 kg (BMI 38.4 ± 5.5 kg/m^2). Of the study participants, 70.6% were women.

Ketonemia levels

Ketonemia levels were evaluated throughout the intervention weekly (Additional file 1: Fig. S1). As expected, the control group (MedDiet) showed the lowest values of ketone bodies during the whole study, being different from the rest of the interventions (p value < 0.05). KD was the intervention with the highest increase in ketonemia (p value < 0.05). No significant differences in ketonemia levels were found among eTRE, lTRE, and mADF.

Changes in body weight

Within-group changes in body weight from baseline to 1, 2, and 3 months are shown in Table 2. We observed significant weight loss after all the interventions. Therefore, a mean reduction of − 8.4 kg (− 9.5 to − 7.3 kg) was found in the control group at the end of the study, − 11.9 kg (− 12.7 to − 11.1 kg) in KD, − 9.4 kg (−10.4 to − 8.5 kg) in eTRE, − 10.6 kg (− 11.7 to − 9.4 kg) in lTRE, and − 11.8 kg (− 13.3 to − 10.4 kg) in mADF.

On the other hand, differences in weight loss between the MedDiet arm and the rest of the study interventions (i.e., KD, eTRE, lTRE, and mADF) at 3 months (primary outcome) are shown in Table 3 and Fig. 2. We observed significant differences in weight loss from baseline to 3 months between KD and the control group [− 3.78 kg (− 5.65 to − 1.91 kg)], between mADF and the control group [− 3.14 kg (− 4.98 to − 1.30 kg)], and between lTRE and the control group [− 2.27 kg (− 4.13 to − 0.40 kg)], but not between eTRE and the control group [− 1.22 kg (− 3.07

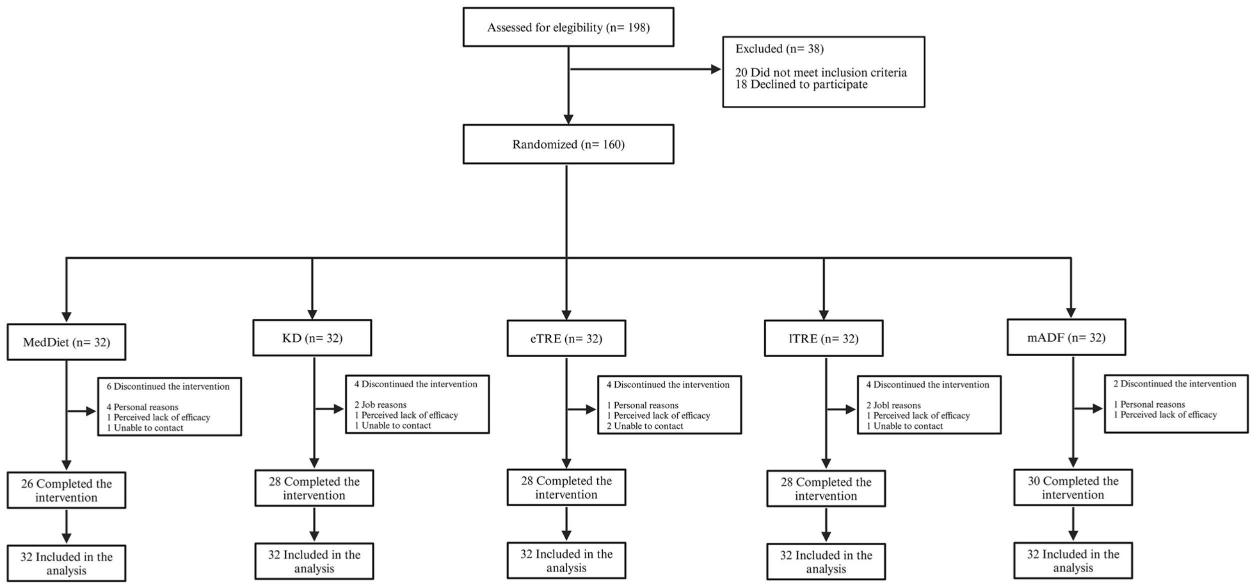

Fig. 1 Flowchart of the study participants. MedDiet, Mediterranean diet; KD, ketogenic diet; eTRE, early time-restricted eating; lTRE, late time-restricted eating; mADF, alternate-day fasting

Table 1 Clinical characteristics of the study participants at baseline

	All (*n* = 160)	MedDiet (*n* = 32)	KD (*n* = 32)	eTRE (*n* = 32)	lTRE (*n* = 32)	mADF (*n* = 32)
Age (years)	45.7 ± 10.7	45.5 ± 12.2	44.9 ± 10.9	45.5 ± 11.1	45.5 ± 11.4	46.9 ± 7.9
Female sex (*n*,%)	113 (70.6)	22 (68.8)	26 (81.3)	25 (78.1)	23 (71.9)	17 (53.1)
Body weight (kg)	107.5 ± 19.5	109.3 ± 21.7	102.8 ± 15.8	103.3 ± 17.1	107.1 ± 19.9	115.1 ± 21.0
Body mass index (kg/m^2)	38.4 ± 5.5	39.1 ± 5.6	37.0 ± 5.6	38.1 ± 5.3	38.2 ± 5.7	39.4 ± 6.2
Body fat mass (kg)	45.5 ± 12.4	46.0 ± 11.2	43.5 ± 10.7	45.2 ± 11.0	43.7 ± 11.6	49.0 ± 16.5
Body lean mass (kg)	61.1 ± 13.9	62.7 ± 15.0	58.4 ± 10.7	56.5 ± 11.4	62.4 ± 15.2	65.5 ± 15.6
Body fat (%)	40.7 ± 5.8	41.3 ± 5.3	41.7 ± 5.9	41.5 ± 4.3	40.4 ± 6.9	38.5 ± 5.9
Waist circumference (cm)	117.1 ± 13.3	118.0 ± 13.9	113.8 ± 12.0	115.3 ± 13.9	117.9 ± 13.9	120.4 ± 13.6
Systolic blood pressure (mmHg)	137.6 ± 16.9	135.7 ± 16.5	141.0 ± 15.9	138.9 ± 16.3	132.5 ± 13.4	139.9 ± 21.5
Diastolic blood pressure (mmHg)	85.6 ± 10.4	85.2 ± 12.0	85.1 ± 9.6	87.2 ± 8.2	84.1 ± 8.1	86.3 ± 13.6
Glucose (mg/dl)	95.0 ± 12.2	94.7 ± 11.1	93.0 ± 9.2	94.1 ± 9.3	92.9 ± 10.4	100.6 ± 18.1
Glycated hemoglobin (%)	5.5 ± 0.4	5.4 ± 0.3	5.6 ± 0.5	5.4 ± 0.3	5.4 ± 0.4	5.7 ± 0.5
HOMA-IR	4.7 ± 2.8	5.5 ± 3.7	3.9 ± 1.5	4.1 ± 1.6	4.5 ± 2.5	5.5 ± 3.5
Triglycerides (mg/dl)	122.7 ± 62.9	123.4 ± 92.1	120.4 ± 50.0	109.3 ± 36.8	111.3 ± 42.8	149.2 ± 70.8
Total cholesterol (mg/dl)	189.5 ± 34.0	179.4 ± 27.4	197.6 ± 27.8	188.6 ± 30.0	190.2 ± 38.9	191.7 ± 42.6
HDL-cholesterol (mg/dl)	46.4 ± 10.3	47.3 ± 10.6	48.1 ± 11.0	46.5 ± 9.1	44.9 ± 9.8	44.7 ± 10.9
LDL-cholesterol (mg/dl)	118.9 ± 28.5	109.5 ± 23.3	125.5 ± 25.1	120.2 ± 25.3	122.4 ± 32.0	117.1 ± 34.5
Hypertension (*n*,%)	52 (32.5)	13 (40.6)	10 (31.3)	10 (31.3)	7 (21.9)	12 (37.5)

Data are given as mean ± standard deviation for continuous variables, or percentages for categorical variables. Biochemical parameters were obtained after a 12-h fast.

MedDiet Mediterranean diet, *KD* ketogenic diet, *eTRE* early time-restricted eating, *lTRE* late time-restricted eating, *mADF* modified alternate-day fasting, *HOMA-IR* homeostatic model assessment for insulin resistance, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein

to 0.64 kg)]. Of note, mADF and KD groups showed differences in weight loss from the first and second month, respectively, compared with the control group.

Changes in body composition

Within-group reductions in body fat mass were observed at 3 months after all the interventions (Table 2), although regarding changes in body composition between the

Table 2 Within-group changes in weight and body composition from baseline to 1, 2, and 3 months after the interventions

	MedDiet (*n* = 32)	KD (*n* = 32)	eTRE (*n* = 32)	lTRE (*n* = 32)	mADF (*n* = 32)
Body weight (% lost)					
1 month	4.40 (3.55 to 5.24)	5.87 (5.19 to 6.55)	5.51 (4.72 to 6.31)	5.08 (4.21 to 5.95)	5.85 (4.78 to 6.92)
2 months	6.32 (5.47 to 7.16)	9.17 (8.45 to 9.88)	7.89 (7.05 to 8.74)	7.95 (7.07 to 8.83)	9.12 (8.04 to 10.21)
3 months	7.73 (6.78 to 8.69)	11.63 (10.89 to 12.36)	9.16 (8.32 to 10.00)	9.87 (8.94 to 10.81)	10.04 (8.93 to 11.15)
p-value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Body weight (kg)					
1 month	− 4.71 (− 5.67 to − 3.75)	− 6.05 (− 6.81 to − 5.28)	− 5.68 (− 6.58 to − 4.78)	− 5.19 (− 6.26 to − 4.12)	− 6.91 (− 8.31 to − 5.51)
2 months	− 6.83 (− 7.78 to − 5.87)	− 9.39 (− 10.20 to − 8.59)	− 8.06 (− 9.01 to − 7.10)	− 8.44 (− 9.53 to − 7.35)	− 10.75 (− 12.17 to − 9.32)
3 months	− 8.41 (− 9.49 to − 7.32)	− 11.91 (− 12.73 to − 11.08)	− 9.43 (− 10.38 to − 8.47)	− 10.56 (− 11.71 to − 9.40)	− 11.80 (− 13.25 to − 10.35)
p-value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Body mass index (kg/m^2)					
1 month	− 1.91 (− 2.29 to − 1.53)	− 2.28 (− 2.69 to − 1.87)	− 2.30 (− 2.71 to − 1.89)	− 1.88 (− 2.42 to − 1.35)	− 2.32 (− 2.80 to − 1.83)
2 months	− 2.58 (− 2.95 to − 2.21)	− 3.79 (− 4.22 to − 3.37)	− 3.45 (− 3.87 to − 3.02)	− 2.85 (− 3.41 to − 2.30)	− 3.71 (− 4.20 to − 3.23)
3 months	− 3.05 (− 3.47 to − 2.63)	− 4.34 (− 4.77 to − 3.92)	− 3.70 (− 4.12 to − 3.27)	− 4.17 (− 4.75 to − 3.59)	− 4.00 (− 4.49 to − 3.50)
p-value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Body fat mass (kg)					
1 month	− 3.22 (− 4.66 to − 1.78)	− 3.71 (− 4.98 to − 2.45)	− 6.04 (− 7.80 to − 4.27)	− 3.20 (− 4.37 to − 1.67)	− 8.02 (− 11.19 to − 4.85)
2 months	− 5.89 (− 7.36 to − 4.42)	− 8.26 (− 9.63 to − 6.89)	− 8.56 (− 10.39 to − 6.72)	− 5.48 (− 6.83 to − 4.12)	− 12.50 (− 15.75 to − 9.26)
3 months	− 6.34 (− 8.01 to − 4.67)	− 8.51 (− 9.94 to − 7.07)	− 10.00 (− 11.88 to − 8.12)	− 7.82 (− 9.25 to − 6.38)	− 14.26 (− 17.63 to − 10.89)
p-value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Body lean mass (kg)					
1 month	− 0.92 (− 2.35 to 0.51)	− 1.69 (− 2.93 to − 0.44)	0.67 (− 1.82 to 3.16)	− 3.31 (− 5.16 to − 1.45)	1.04 (− 2.27 to 4.36)
2 months	− 0.37 (− 1.83 to 1.10)	− 0.39 (− 1.75 to 0.96)	− 0.58 (− 3.17 to 2.01)	− 1.75 (− 3.61 to 0.11)	1.26 (− 2.13 to 4.65)
3 months	− 0.95 (− 2.61 to 0.72)	− 2.12 (− 3.53 to − 0.71)	2.41 (− 2.44 to 5.06)	− 3.82 (− 5.80 to − 1.85)	1.30 (− 2.30 to 4.90)
p-value	0.417	0.055	0.353	0.024	0.668

Data are shown as mean (95% confidence interval). *P* values of within-group changes from baseline to varying time points were calculated using linear mixed models adjusted by time points, age (years), sex (indicator) and baseline measurement.

MedDiet Mediterranean diet, *KD* ketogenic diet, *eTRE* early time-restricted eating, *lTRE* late time-restricted eating, *mADF* modified alternate-day fasting

MedDiet and the rest of the interventions, only the eTRE and mADF groups showed greater decreases in fat mass as compared with the control group (Table 3). No differences between the control group and the rest of the interventions regarding changes in body lean mass were found.

Changes in cardiometabolic risk factors

Other secondary outcomes of this trial included the assessment of changes in cardiometabolic risk factors from baseline to 3 months. We found no significant differences between the MedDiet and the rest of the interventions for fasting glucose, HOMA-IR, triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, systolic blood pressure, or diastolic blood pressure at 3 months (Table 4). However, when weight loss was included in the model for adjustment, we observed significantly lower decreases in diastolic blood pressure in KD and lTRE compared with the MedDiet, and significant increases in HDL cholesterol in mADF compared with the MedDiet at the end of the trial (Additional file 2: Table S1).

Safety

No deaths or serious adverse events during the trial were reported.

Discussion

In this randomized clinical trial, we show that both a calorie-restricted MedDiet and other alternative calorie-restricted dietary interventions, such as a very-low-carbohydrate diet (KD), TRE, or intermittent fasting, could be effective strategies to promote weight loss in patients with obesity in the short term (3 months). However, our findings suggest that a KD, mADF, or lTRE may lead to more weight loss, as compared with MedDiet. Given that direct comparisons between calorie-restricted MedDiet and other calorie-restricted alternative dietary approaches are lacking, our results add valuable

Table 3 Coefficients of linear mixed models[1] for the comparison of each repeated outcome across time between the control group (Mediterranean diet) and the different intervention groups. Primary outcome analysis: differences in weight loss from baseline to 3 months between the control group (Mediterranean diet) and the different intervention groups

	KD (*n* = 32)	eTRE (*n* = 32)	lTRE (*n* = 32)	mADF (*n* = 32)
Body weight (kg)				
1 month	− 1.54 (− 3.27 to 0.19)	− 1.21 (− 2.94 to 0.52)	− 0.51 (− 2.24 to 1.22)	**− 1.92 (− 3.65 to − 0.19)**
2 months	**− 2.84 (− 4.62 to − 1.07)**	− 1.51 (− 3.27 to 0.26)	− 1.67 (− 3.41 to 0.07)	**− 3.62 (− 5.40 to − 1.88)**
3 months	**− 3.78 (− 5.65 to − 1.91)**	− 1.22 (− 3.07 to 0.64)	**− 2.27 (− 4.13 to − 0.40)**	**− 3.14 (− 4.98 to − 1.30)**
Body mass index (kg/m^2)				
1 month	− 0.48 (− 1.21 to 0.25)	− 0.44 (− 1.17 to 0.29)	− 0.01 (− 0.74 to 0.71)	− 0.38 (− 1.11 to 0.35)
2 months	**− 1.34 (− 2.08 to − 0.59)**	**− 0.94 (− 1.68 to − 0.21)**	− 0.31 (− 1.04 to 0.42)	**− 1.06 (− 1.79 to − 0.34)**
3 months	**− 1.41 (− 2.19 to − 0.63)**	− 0.67 (− 1.46 to 0.09)	**− 1.17 (− 1.94 to − 0.39)**	**− 0.89 (− 1.65 to − 0.12)**
Body fat mass (kg)				
1 month	− 1.30 (− 4.48 to 1.88)	− 3.01 (− 6.24 to 0.05)	− 0.53 (− 3.71 to 2.64)	**− 3.80 (− 6.94 to − 0.67)**
2 months	− 2.97 (− 6.29 to 0.34)	− 2.80 (− 6.02 to 0.05)	− 0.15 (− 3.35 to 3.05)	**− 5.59 (− 8.76 to − 2.41)**
3 months	− 2.83 (− 6.38 to 0.72)	**− 3.73 (− 7.14 to − 0.31)**	− 1.98 (− 5.43 to 1.47)	**− 6.57 (− 9.97 to − 3.17)**
Body lean mass (kg)				
1 month	− 1.41 (− 4.74 to 1.93)	0.30 (− 3.01 to 3.61)	− 2.19 (− 5.55 to 1.18)	1.90 (− 1.40 to 5.21)
2 months	− 0.51 (− 4.00 to 2.98)	− 1.59 (− 4.98 to 1.80)	− 1.15 (− 4.54 to 2.23)	1.79 (− 1.57 to 5.14)
3 months	− 1.67 (− 5.42 to 2.08)	1.92 (− 1.70 to 5.53)	− 2.88 (− 6.56 to 0.79)	2.38 (− 1.25 to 6.02)

Data are given as mean (95% confidence intervals).[1]Adjusted by time points (dummies with initial time as reference category), age (years), sex (indicator), baseline measurement and time points and group (dummies with control diet as reference group) interaction terms. Only regression coefficients for the time points and group interaction terms are shown.

MedDiet Mediterranean diet, *KD* ketogenic diet, *eTRE* early time-restricted eating, *lTRE* late time-restricted eating, *mADF* modified alternate-day fasting

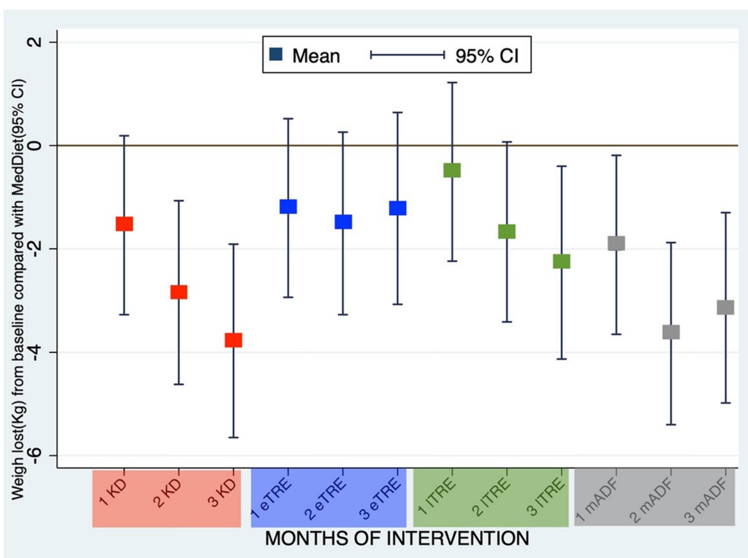

Fig. 2 Differences in weight loss from baseline to 1, 2, and 3 months between the control group (Mediterranean diet) and the different intervention groups. MedDiet, Mediterranean diet; KD, ketogenic diet; eTRE, early time-restricted eating; lTRE, late time-restricted eating; mADF, alternate-day fasting

information to previous research, contributing to the advance of obesity treatment approaches, and may highlight the need for healthcare providers to consider other alternative nutritional strategies as part of obesity management.

We found that both KD and mADF may be effective dietary interventions for weight loss in the short term. Previously, Yancy et al. showed that a calorie-unrestricted KD resulted in greater weight loss in patients with obesity, compared with a calorie-restricted low-fat

Table 4 Changes in cardiometabolic risk factors from baseline to three months between the control group (Mediterranean diet) and the different intervention groups

	KD (*n* = 32)	eTRE (*n* = 32)	lTRE (*n* = 32)	mADF (*n* = 32)
Glucose (mg/dl)	− 4.29 (− 10.15 to 1.56)	− 4.34 (− 10.19 to 1.52)	2.13 (− 3.79 to 8.04)	− 4.14 (− 10.05 to 1.77)
HOMA-IR	− 2.46 (− 5.21 to 0.30)	− 2.22 (− 4.97 to 0.52)	− 1.36 (− 4.14 to 1.42)	− 2.38 (− 5.14 to 0.37)
Triglycerides (mg/dl)	− 10.41 (− 33.53 to 12.70)	− 10.43 (− 33.63 to 12.76)	− 10.41 (− 33.83 to 13.01)	− 21.12 (− 44.44 to 2.12)
Total cholesterol (mg/dl)	0.93 (− 12.99 to 14.85)	− 3.47 (− 17.43 to 10.50)	− 2.56 (− 16.66 to 11.55)	− 0.12 (− 14.16 to 13.93)
HDL-cholesterol (mg/dl)	1.36 (− 2.90 to 5.62)	2.26 (− 2.02 to 6.53)	0.01 (− 4.31 to 4.33)	3.97 (− 0.33 to 8.27)
LDL-cholesterol (mg/dl)	2.29 (− 10.02 to 14.60)	− 2.92 (− 15.26 to 9.42)	0.24 (− 12.23 to 12.70)	0.42 (− 12.00 to 12.84)
Systolic blood pressure (mmHg)	− 6.83 (− 14.57 to 0.90)	− 0.66 (− 8.27 to 6.95)	− 0.96 (− 8.63 to 6.71)	− 2.34 (− 9.88 to 5.20)
Diastolic blood pressure (mmHg)	3.10 (− 0.82 to 7.02)	− 0.56 (− 4.41 to 3.30)	3.18 (− 0.71 to 7.07)	1.39 (− 2.43 to 5.21)

Data are given as mean (95% confidence intervals). Linear mixed models were adjusted by time points (dummies with initial time as reference category), age (years), sex (indicator), baseline measurement and time points and group (dummies with control diet as reference group) interaction terms. Only regression coefficients for the time points and group interaction terms are shown. Biochemical parameters were obtained after a 12-h fast.

MedDiet Mediterranean diet, *KD* ketogenic diet, *eTRE* early time-restricted eating, *lTRE* late time-restricted eating, *mADF* modified alternate-day fasting, *HOMA-IR* homeostatic model assessment for insulin resistance, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein

diet [10]. Recently, in a 6-month trial, a calorie-unrestricted low-carbohydrate diet was demonstrated to have greater effects on weight loss than a high-carbohydrate, low-fat diet in patients with obesity and type 2 diabetes [23]. Consistent with our study, these results suggest that KD diets may be superior for weight loss compared to other nutritional strategies, although other studies have reported no significant differences [24]. Notably, our control group consisted of a calorie-restricted MedDiet, which underscores the uniqueness of our study design. On the other hand, in a 2-year trial including 366 patients with obesity (86% men), Shai et al. showed that weight loss was similar with a low-carbohydrate diet without calorie restriction and a calorie-restricted MedDiet [11]. However, some differences from our study (such as calorie-restriction patterns) should be considered.

On the other hand, mADF was shown to be effective for weight loss in previous trials, although evidence is still limited and no studies have directly compared this intervention with MedDiet, as ours did. In line with our results, mADF was superior to daily calorie restriction in an 8-week randomized trial including patients with metabolic syndrome [25]. However, mADF did not produce greater effects on weight loss than daily calorie restriction in a 12-month trial conducted in 100 patients with obesity [16].

It was noteworthy that the two interventions with the greatest effects on weight loss in our study (i.e., the KD and mADF) achieved higher ketonemia levels during the trial. In this regard, nutritional ketosis might lead to weight loss through several mechanisms [26, 27]. However, these hypotheses should be confirmed in future trials that incorporate validated and specific tools and strategies for these nutritional interventions to achieve the most objective dietary assessment possible. It has also been suggested that additional mechanistic insights may be considered to explain weight loss and other metabolic benefits of nutritional ketosis [28]. Indeed, lowering carbohydrate intake has been associated with an increased energy expenditure [29]. Nevertheless, this point was not evaluated in our study, and further research is needed to elucidate the mechanisms leading to weight loss in relation to these interventions.

We also observed that the late modality of TRE (lTRE) with calorie restriction may be superior to the calorie-restricted MedDiet in terms of weight loss. Mixed results have been reported regarding the effects of TRE on weight loss. In the randomized clinical trial by Liu et al., including 139 patients with obesity, there were no significant differences between eTRE with calorie restriction or daily calorie restriction [14]. However, Jamshed et al. recently reported that eTRE with calorie restriction was more effective than eating the same calorie restriction over a window of $\geq$ 12 h [15]. On the other hand, only a few studies have made direct comparisons between the metabolic effects of lTRE and eTRE. In this regard, a trial conducted in subjects with overweight and obesity found no differences in weight loss between eTRE and lTRE [30]. Of note, in our study, only reductions in body fat mass were achieved after the eTRE intervention (but not after the lTRE intervention) as compared with the MedDiet, which suggests that meal timing in TRE may have an important role. Further investigation is needed to confirm these findings and to elucidate the potential mechanisms involved in these results. Interestingly, some studies have reported that the combination of TRE with a low-carbohydrate diet induces more weight loss than these interventions alone [31]. Therefore, future approaches may include the evaluation of the efficacy of the combination of different dietary strategies.

Changes in body composition were also evaluated in this trial. Despite the fact that all diets were associated with reductions in fat mass, only eTRE and mADF showed differences with respect to the control group. In fact, mADF was associated with the highest decrease in body fat mass at the end of the study. Nevertheless, in contrast to our results, Trepanowski et al. reported no differences in body composition between mADF and daily calorie restriction [32], nor did Jamshed et al. between eTRE and daily calorie restriction at the end of the study [15]. These discrepancies might be related to the characteristics of our control intervention, as a MedDiet with calorie restriction was not evaluated in previous studies.

Regarding the changes in cardiometabolic risk factors after the interventions, no between-group differences regarding the MedDiet and the rest of the study interventions were found at 3 months for cardiometabolic parameters. However, some differences were detected between the MedDiet and KD/lTRE for diastolic blood pressure, and with mADF for HDL cholesterol levels when weight loss was included in the model for adjustment. Previous evidence has shown that both the MedDiet and different dietary approaches (i.e., low-carbohydrate diets, TRE, or intermittent fasting) can improve cardiometabolic risk factors [8, 33–35]. Nevertheless, direct comparisons between MedDiet and the nutritional interventions evaluated in this trial are scarce, especially for TRE or mADF. Previously, the trial by Shai et al. reported the greatest increase in HDL cholesterol and decrease in triglycerides in the low carbohydrate diet without calorie restriction, compared with a calorie-restricted MedDiet or calorie-restricted low-fat diet in patients with obesity, without differences in plasma glucose levels or blood pressure [11]. A crossover trial conducted in patients with type 2 diabetes following a KD and MedDiet showed no differences in HbA1c and a greater decrease in triglycerides (with an increase in LDL cholesterol) in KD [36]. While the current study was able to show differences in weight loss efficacy between diet counseling approaches, the data cannot support clear conclusions about differences between diets regarding cardiometabolic risk factors independent of weight loss and energy intake. Moreover, any potential improvements observed might have been mediated by differences in self-selected energy intake and compliance with the assigned protocols. Therefore, these findings should be interpreted with caution, and devoted trials comparing the MedDiet and these alternative dietary approaches, primarily focused on the different cardiometabolic outcomes, are needed.

This study has some limitations. First, it should be noted that changes in body weight were only evaluated in the short term (3 months), and different findings might have been observed after longer follow-up. Therefore, further long-term trials are needed to evaluate the effects of these dietary interventions. Also, these results cannot be generalized to other populations, including patients with diabetes and people from other races or ethnicities. Despite the fact that a close patient follow-up was performed during the trial and personalized, written daily meal plans were provided to the study participants, and ketonemia levels were monitored in all arms during the study, no specific tools of self-reported dietary intake were used in this study, which constitutes a limitation. Multiple secondary outcomes were assessed in this study, which should be considered as hypothesis-generating. Finally, although bioelectrical impedance analysis is the most common method for the assessment of body composition in clinical practice, we acknowledge that this technique is less precise than dual X-ray absorptiometry (DXA). On the other hand, an important strength of this study was its design, a randomized clinical trial, also including a close follow-up and an important sample size as compared with previous studies. Moreover, to our knowledge, this is the first trial that compares three different calorie-restricted emerging dietary approaches with a calorie-restricted MedDiet.

Conclusions

In this 3-month trial, we show that a calorie-restricted KD, mADF, or lTRE may be more effective than a calorie-restricted MedDiet in terms of weight loss in patients with obesity. Further research is needed to evaluate the long-term feasibility and efficacy of these dietary interventions compared with the MedDiet.

Abbreviations

BMI	Body mass index
eTRE	Early time-restricted eating
HbA1c	Glycated hemoglobin
HDL	High-density lipoprotein
HOMA-IR	Homeostasis model assessment of insulin resistance
LDL	Low-density lipoprotein
lTRE	Late time-restricted eating
mADF	Modified alternate-day fasting
MedDiet	Mediterranean diet
KD	Ketogenic diet
REML	Restricted maximum likelihood
SD	Standard deviation
TRE	Time-restricted eating

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-04182-z.

Additional file 1. Fig. S1. Mean ketonemia levels during the trial in the different groups. MedDiet, Mediterranean diet; KD, ketogenic diet; eTRE, early time-restricted eating; lTRE, late time-restricted eating; mADF, alternate-day fasting.

Additional file 2. Table S1. Changes in cardiometabolic risk factors from baseline to three months between the control group (Mediterranean diet) and the different intervention groups including weight loss adjustments.

Acknowledgements
Ketogenic replacement for the first meal in KD and 24-h fast day in mADF were provided by PronoKal Health Group. PronoKal was not involved in this study outside of providing replacement meals for the KD and mADF arms.

Authors' contributions
I.M.-I., and F.J.T.: conceptualization and study design; J.I.M.-M., B.B., A.M.G.-P., and I.M.-I.: data collection; J.I.M.-M., B.B., M.G.-B., and F.J.T: data analysis and interpretation; J.I.M-M. and B.B.: original draft preparation; J.I.M.-M., M.G.-B, A.M.G.-P., M.M.-G., I.M.-I., and F.J.T.: manuscript review and editing; F.J.T.: supervision.

Funding
This study received a grant support from Instituto de Salud Carlos III (ISCIII) (PI18/01160). J.I.M.-M. was supported by a Rio Hortega grant and a Juan Rodés grant from Instituto de Salud Carlos III, Madrid, Spain (CM22/00217; JR24/00006). A.M.G.-P. was supported by a Long-term reinforcement research contract from Servicio Andaluz de Salud (B-0033–2014). M.M.-G. was the recipient of the Nicolas Monardes Programme from the "Servicio Andaluz de Salud, Junta de Andalucia", Spain (RC-0001-2018 and C-0029-2014). I.M.-I. was supported by a Miguel Servet type II grant from Instituto de Salud Carlos III, Madrid, Spain (CPII21/00013). The funding source had no role in the study design, data collection, statistical analysis, manuscript preparation/interpretation, or the decision to submit this paper for publication.

Data availability
The datasets generated and analysed during the current study are not publicly available due to ethical considerations and terms of informed consent, but are available from the corresponding authors on reasonable request, under appropriate agreements and ethical considerations.

Declarations

Ethics approval and consent to participate
This study was conducted according to the principles of the Declaration of Helsinki, and was reviewed and approved by the Ethics Research Committee of Virgen de la Victoria University Hospital (Málaga, Spain) (ID 1/2019-P14). All participants gave their written informed consent to participate in this study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 6 December 2024 Accepted: 2 June 2025
Published online: 01 July 2025

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