Modified alternate-day fasting vs. calorie restriction in the treatment of patients with metabolic syndrome: A randomized clinical trial

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Modified Alternate-Day Fasting vs. Calorie Restriction in the Treatment of Patients with Metabolic Syndrome: A Randomized Clinical Trial

Abstract:

Objective: The aim of present study was to compare the effect of calorie restriction and modified alternate-day fasting diet on treatment of adults with metabolic syndrome.

Design: This randomized clinical trial was conducted on 70 participants diagnosed with metabolic syndrome.

Setting: Patients were randomly allocated into 2 groups to follow either calorie restriction or a modified alternate-day fasting diet for 8 weeks. Diets was prescribed by dietitians and specialized for each participant. Anthropometric parameters, blood pressure, fasting plasma glucose, fasting insulin, HOMA-IR and lipid profile were measured at baseline and after trial conclusion.

Results: 69, out of 70, participants completed the study and were included in the final analysis. The results showed that, compared with calorie restriction, following the modified alternate-day fasting diet significantly reduced body weight (P= 0.003), waist circumference (P= 0.026), systolic blood pressure (P= 0.029) and fasting plasma glucose (P= 0.009). However, no significant difference was observed between the 2 groups in triglyceride (P= 0.614), total cholesterol (P= 0.759), LDL-C (P= 0.289), HDL-C (P=0.909), diastolic blood pressure (P=0.262), HOMA- IR (P= 0.425) and fasting insulin concentrations (P= 0.496). In addition, the participants did not report any complaint due to difficulties with diet adherence when following calorie restriction or modified alternate-day fasting diet.

Conclusions: the present study suggests that modified alternate-day fasting diet may be a more effective option in managing body weight, waist circumference, systolic blood pressure, and fasting plasma glucose, compared with common calorie restriction. Further studies are needed to confirm the veracity of our results.

Keywords: Alternate-day fasting, energy restriction, anthropometric, glycemic index, plasma lipids, metabolic

syndrome x

Introduction

Metabolic syndrome (MetS) is a highly prevalent metabolic disorder which is defied by a set of several interrelated cardiometabolic risk factors, such as abdominal obesity, insulin resistance, hyperglycemia, hypertension and dyslipidemia (elevated triglyceride (TG) levels and low high-density lipoprotein cholesterol (HDL-C) (1). Although there is debate surrounding the concept of MetS, it is demonstrable that MetS is a major and prevalent risk factor for incidence of cardiovascular disease and diabetes (2). It has been reported that risk for atherosclerotic cardiovascular disease and type 2 diabetes are double and fivefold, respectively, among patients with MetS (3). In addition to metabolic and genetic susceptibilities, diet and physical activity are important factors, and MetS occurs more often among those who consume excessive nutrients, have an unhealthy dietary pattern, and are physically inactive (4, 5). Sedentary lifestyle and consumption of a high-calorie diet has lead to an increased prevalence of MetS in recent decades and makes it a critical problem faced by health care system (6). Several strategies are suggested for the management of MetS. Changing lifestyle (diet and physical activity) is regarded a cornerstone and first step to control metabolic disorders involved with this syndrome (7, 8). Moreover, several dietary strategies have been investigated during recent years (9-11).

Calorie restriction (CR) diet, decreasing energy intake by 15 to 40% of daily needs (12), is a common dietary manipulation for weight loss, and frequently uses for clinical practices. Although the positive result of CR diet has been documented among several diseases in which obesity/overweight is known as a risk factor (13, 14), the compliance of the diet by patients over long periods is usually low. Another dietary strategy that may be more feasible than CR diet in practice is an Alternate Day Fasting (ADF) regimen which consists of a "fast day" where intake is limited to 25% of the individual's energy needs (approximately 500 calories), alternating with a "feed day" where food is consumed ad-libitum (15, 16). Compared to CR, ADF diet has exhibited greater participant compliance firblonger periods (17), and beneficial effect of ADF on healthy, diabetic and cardiovascular disease patients has been reported in several studies. However, there is currently a lack of sufficient data regarding the influence of these diets on MetS. Therefore, the present study sought to compare the therapeutic effect of ADF and CR dietary intervention on patients with MetS.

Method

Participants:

This study was a single-center, randomized clinical trial that was conducted from December 2015 to March 2016 among patients with Mets, referres to Sediqe-Tahere Heart Center, Isfahan, Iran. MetS was diagnosed according to the Revised National Cholesterol Education Program Third Adult Treatment Panel (RNCEP: ATPIII) definition (18). The patients were eligible to enter the study if they were aged 25-60 and overweight (25 ≤BMI ≤ 40 kg/m^2). Individuals with weight changes ≥5% for 3 months preceding the study, history of liver cardiovascular, renal, and metabolic disease, smoking or taking any medication or following a special diet in the last 6 months, which is known to impact on body weight, serum lipids, or glucose metabolism, breast feeding, post-menopausal and pregnant women were excluded. Sample size was estimated by thebformula represented for parallel clinical trials, considering type 1 error (α) of 0.05 and type 2 errors (β) of 0.2. The TG serum levels was assumed as the key variable, and the difference in mean and SD of TG concentration was based on a previous study (11). With consideration for 20%, drop-out, the final sample size was determined to be 35 participants per group. The present study protocol was confirmed by the Ethics Committee of Isfahan University of Medical Science and was registered in the Iranian registry of clinical trials (http://www.irct.ir: IRCT201509092395N8). The study was also performed based on the CONSORT statement recommendation (19).

Study design

At the beginning, eligible participants entered to 2-weeks run-in period. After explanation of the goal and nature of the study, individuals were asked to complete the ethical consent form. Then, participants were stratified according to baseline BMI, age and sex, and randomly assigned in a 1:1 ratio into ADF or CR group to receive and follow their special diet for 8-weeks. Randomization was performed by using by computer-generated random numbers and was concealed from the researchers as well as participants. Patients were asked to preserve their regular physical activity levels and avoid to intake any supplements or medication which interfere with outcome of interest throughout the trial period. A physical activity questionnaire (20) and a 3-days dietary record (over two weekdays and one weekend day) was completed by participants at baseline and end of trials. In addition, participants were monitored in weekly phone interviews.

Diet protocol

All participants were instructed to follow their special diet which was prescribed based on their group and total energy need. The energy requirements for the individuals were calculated using the Mifflin equation (21). Patients in the ADF group were asked to consume a very low calorie diet (75% energy restriction) during the 3 fast days (Saturday, Monday, Wednesday) and then ate a diet that providing 100% of their energy needs on each feed day (Sunday, Tuesday, Thursday). On Friday, subjects were able consume ad-libitum without limitation. The feed and fast days began at midnight each day, and all fast day meals were consumed between 12.00 pm and 2.00 pm to ensure that each subject was undergoing the same duration of fasting. Subjects were permitted to consume calorie-free foods (such as water, green tea, coffee without sugar (< 400 mg caffeine per day), non-starchy vegetable (such as lettuce, cucumber, green leaf, tomato) and sugar free gums on the fast day and were encouraged to drink plenty of water. In the CR group, subjects consumed 75% of their energy needs each day. All subjects in the two groups were required to prepare all of their meals at home. Control and intervention group subjects were informed to maintain their regular physical activity habits all over the duration of the investigation. Subjects were also instructed to prepare healthy food choices, by selecting low fat meat and dairy options and increasing fruit and vegetable intake. Daily dietary carbohydrate, fat and protein accounted for 52, 30 and 18% of ingested energy, respectively.

Assessment of variables

Fasting blood samples were acquired to measure cholesterol, Triglycerides (TG), High- Density Lipoprotein Cholesterol (HDL-C), Low- Density Lipoprotein Cholesterol (LDL- C), Fasting Plasma Glucose (FPG), Fasting Insulin (FI). Participants were fasted for 12 h and samples were obtained between 7.00 am to 9.00 am at baseline and post-treatment (week 10) for biochemical analysis. Blood was centrifuged for 10 min at 520 × g at 4 ˚C to separate plasma from RBCs, and was stored at -70 ˚C until further analysis. FPG concentrations were measured using auto-analyzer (glucose oxidase/peroxidase). Plasma TC, HDL-C, and TG concentrations were measured in duplicate using cholesterol oxidase/peroxidase, detergent and glycerol phosphate oxidase/peroxidase methods, respectively. LDL-C concentration was calculated using the Friedwald equation (LDL-C= total cholesterol – TG/ 2.18 – HDL-C). Plasma insulin levels were measured by Elisa method (Pars Azmoon, Iran; intra- assay variation, 4.6%; inter- assay variation, 6%). Insulin resistance was calculated according the Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) equation: fasting glucose (mmol/L) * fasting insulin (µU/L)/ 22.5. At each visit blood pressure was measured with a digital automatic blood pressure device (Omron HEM 705 LP, Kyoto, Japan) in a seated position after a 10-minute rest.

Body weight and height of each participant were assessed at the baseline and end of trial while wearing minimal clothing and unshod by a trained researcher. Waist circumstance (WC) was measured by a flexible tape to the nearest 0.1 cm, with the participant standing, at the midway between the lower costal margin of the last palpable rib and the top of the iliac crest during a period of expiration, and BMI was calculated as weight in kilograms divided by height in meters squared.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software version 20 (SPSS Inc., Chicago, USA). The Kolmogorov-Smirnov test was used to check the normal distribution of data. Independent samples t-test and chi-square was applied to compare the difference among continuous and categorical variables between 2 groups at baseline, respectively. Analysis of covariance (ANCOVA) was used to detect the difference of variable changes between 2 groups after intervention. Data was presented as mean ± standard deviation (SD) for continues variables and P values <0.05 were considered statistically significant.

Results

Of 105 subject which were primarily assessed for inclusion/exclusion criteria, 70 patients were eligible and randomly assigned to either ADF or CR groups. Only one patient from the CR group was excluded due to being lost to follow up. Therefore, 69 participants (ADF=35 and CR=34) completed the trial and were included to final analysis (**Figure 1**). No significant difference was found between two groups in term of age, sex, body weight, WC, systolic blood pressure (SBP), diastolic blood pressure (DBP), physical activity at baseline of the study **(Table 1)**. In addition, based on 3-days dietary record, no statistically significant difference was seen in energy intake and macronutrient components between 2 group at baseline **(Table 2).** No harmful reactions or adverse events were reported throughout the study.

The results of this study show that a significant reduction was detected in body weight (kg) (-4.1±3.65 vs -1.7±1.49; P=0.003), WC (cm) (-4±4.09 vs -1±3.44; P=0.026), SBP (mm Hg) (-13±4.00 vs -1±14.42; P=0.029) and FPG (mg/dl) (-5±6.82 vs 0±6.85; P=0.009) after ADF intervention in compare with CR. Whilst, we failed to find any significant changes in BMI (kg/m^2) (-1.6±2.07 vs -0.8±0.90; P=0.060), TG (mg/dl) (-52±90.56 vs -40±78.02; P=0.614), TC (mg/dl) (-11± 24.59 vs -8 ± 31.09; P=759), LDL-C (mg/dl) (-5±20.26 vs 0±21.40; P=0.289), HDL-C (mg/dl) (-1±10.48 vs 0±9.35; P=909), DBP (mm Hg) (-8±7.72 vs -5±12.18; P=0.262), fasting insulin (µU/ml) (-2.41±3.21 vs -1.56±5.41; P=0.496) and HOMA-IR (-0.72±0.92 vs -0.39±1.80; P=0.425) between 2 groups **(Table 3)**.

Discussion

The present study evaluated the effect of following a ADF diet in comparison to CR on adults with MetS for 8-weeks. The results demonstrated that in comparison to a CR diet, adherence to an ADF diet has a more beneficial effect on reducing body weight and WC, and improving in SBP and FPG levels. However, findings of the present study do not suggest any difference between following ADF and CR diet on BMI, lipid profile, DBP, HOMA-IR and fasting insulin concentrations.

MetS has become a major public-health problem and, besides lifestyle-based modification, no effective preventative approach has been documented. In this regard, normalization of body weight and improvement of blood pressure, blood lipids levels, and blood glucose concentration are the main factors in preventing or delaying the development of MetS; particularly in susceptible populations, and the progression to type 2 diabetes or cardiovascular disease in individuals with MetS. Our findings demonstrated that intervention with an ADF diet may be more effective in reducing body weight and WC, as compared to atm CR diet. The same results were found by other studies, for instance, klempel et al (22) and Eshghinia et al (12) reported that following ADF diet resulted in 4 kg weight loss after 8 weeks in overweight individuals. It is suggested that even greater weight loss (5.6 ± 1kg) can be attained by ADF interventions in trials with longer durations (16). It has been shown that the weight loss manifest from ADF is mainly from fat-mass reduction, whilst fat-free mass is generally preserved during ADF (23). Furthermore, greater reduction of WC in the ADF diet, which is known as an indirect indicator of visceral fat mass (12), has been reported previously (14). This marked difference between the 2 prescribed diets in achieving weight loss might be attributable to differences in energy intake betwern ADF and CR. Because ADF studies require subjects to fast 3-4 d/w, greater weight loss is often seen in such trials compared with CR studies (14). Energy balance plays a managing role in body weight changes (24), and given that during fasting, glucose is less available, fat is regarded as a major source for energy, and hence, reduction in body weight and body fat mass will occur (25).

Studies have suggested that long-lasting modifications in manifest during fasting result in various changes in metabolism (26). The results of present study revealed that ADF produces superior changes in improving FPG levels when compared to CR. In accordance with our results, Eshghinia et al. (27) found that FPG significantly reduces from baseline following 4 weeks ADF in obese women. The cause of lower FPG levels is unclear, but may conceivably be due to the number of fasting days performed in the ADF intervention (3-4 fast days) compared to the CR, and therein facilitate the body to use more fatty acid as metabolic fuel. Although a greater reduction in fasting insulin levels and HOMA-IR were detected in the ADF group, these changes did not reach statistical significance when compared with CR. Our findings are in accordance with previous studies (16, 28-32) in which the effect of an ADF diet, either alone or in comparison with a normal diet, on fasting insulin, and a 20-31% reduction in insulin concentrations, after treatment with ADF, was reported. The grade to which fasting insulin is reduced may be correspondent with the amount of weight loss. Hence, studies show that there may be a dose-response association among weight loss and fasting insulin reducing (14). Bhutani et al, showed that intervention with an ADF diet resulted in body weight declinea of 4% from baseline, which caused moderate decreases in HOMA-IR (9%) (28). It seems that the reduction in HOMA-IR by ADF and CR might be associated with the degree of imposed energy restriction and amount of weight loss (14).

Although the findings of the present showed a significant reduction in TG and TC levels from baseline values after ADF intervention, this change did not yield a significant difference when compared to the CR group. An observational study, including 1422 participants and one-year follow-up, reported a beneficial modulating effect of fasting for 21 days on blood lipid parameters (33). However, clinical trial studies which compare the effect of ADF and CR, have not demonstrated any difference in improving blood lipid parameters (34, 35). The lack of difference between the 2 groups might be due to the relatively short duration of our study, and thus, longer duration diets are necessary to elucidate some differences (34, 35)

The present study found that the effect of ADF diet on SBP is more pronounced in comparison to CR. However, no difference was detected between the 2 groups for DBP. In line with our results, previous studies supported a beneficial effect of fasting on SBP (12, 24, 27, 36, 37). Varady et al. (37) reported a 5.1% decrease in SBP after 8 weeks intervention, whereas DBP did not change. Another study by Eshghinia et al. (27) demonstrated a reduction in both SBP and DBP following 4 weeks ADF intervention in mild to moderately hypertensive women. According to the European society of hypertension, an increase in physical activity (30 min of moderate to intensity physical activity per day) and decrease in body weight are the first line of high blood pressure treatment in patients with metabolic syndrome (38). Thus, the greater blood pressure lowering effect of ADF in the present study might be associated with greater decreases in body weight (39), and/or due to the suppression of catecholamine production

(40), reducing the sympathetic tone and causing blood pressure to reduce.

The present study had some limitations. First, the duration of tne study was relatively short and may have impeded our ability to detect significant changes in some parameters. However, in this short follow-up, we showed the superiority in adherence with ADF diet in MetS treatment. Second, due to the nature of studying dietary intervention, we could not perform trial in a truly blind fashion. Third, the compliance to the prescribed diet was recorded using self-reporting, which might have resulted in misstatements. In order to resolve this bias, we tried to monitor participants through a phone interview during the intervention and completion of a 3-days food record.

Conclusion:

In summary, this study suggests that ADF is a more effective strategy in managing body weight and WC, and reveals superior improvements in SBP and FPG in comparison to CR. These findings indicate that ADF diet may be a more beneficial therapeutic option in managing MetS. With regard to known limitations in compliance with CR diets, ADF presents a promising option, which results in more beneficial effects, in a short time frame. An ADF diet can be regarded useful, not only for metabolic syndrome treatment, but also can be a practical option for other diseases with metabolic factors such as cardiovascular disease (41, 42). Future studies are needed to investigate the long effect of ADF on metabolism and nutrients absorption.

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Conflict of interest:

None.

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