

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

Parvaresh, A., Razavi, R., Yaghooblo, K., Hassanzadeh, A., Mohammadifard, N., Abbasi, B., Safavi, S. M., Hadi, A. & Clark, C.

Author post-print (accepted) deposited by Coventry University's Repository

## Original citation & hyperlink:

Parvaresh, A, Razavi, R, Yaghooblo, K, Hassanzadeh, A, Mohammadifard, N, Abbasi, B, Safavi, SM, Hadi, A & Clark, C 2019, 'Modified alternate-day fasting vs. calorie restriction in the treatment of patients with metabolic syndrome: A randomized clinical trial', *Complementary Therapies in Medicine*, vol. 47, 102187.

<https://dx.doi.org/10.1016/j.ctim.2019.08.021>

DOI 10.1016/j.ctim.2019.08.021

ISSN 0965-2299

Publisher: Elsevier

**NOTICE: this is the author's version of a work that was accepted for publication in *Complementary Therapies in Medicine*. Changes resulting from the publishing process, such as peer review, editing, corrections, structural formatting, and other quality control mechanisms may not be reflected in this document. Changes may have been made to this work since it was submitted for publication. A definitive version was subsequently published in *Complementary Therapies in Medicine*, 47, (2019)]**

DOI: 10.1016/j.ctim.2019.08.021

© 2019, Elsevier. Licensed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International <http://creativecommons.org/licenses/by-nc-nd/4.0/>

Copyright © and Moral Rights are retained by the author(s) and/ or other copyright owners. A copy can be downloaded for personal non-commercial research or study, without prior permission or charge. This item cannot be reproduced or quoted extensively from without first obtaining permission in writing from the copyright holder(s). The content must not be changed in any way or sold commercially in any format or medium without the formal permission of the copyright holders.

This document is the author's post-print version, incorporating any revisions agreed during the peer-review process. Some differences between the published version and this version may remain and you are advised to consult the published version if you wish to cite from it.

## **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 defined 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 led 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 used 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 for longer 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, referred to Sediqe-Tahere Heart Center, Isfahan, Iran. MetS was diagnosed according to the Revised National Cholesterol Education Program Third Adult Treatment Panel (RNCEP: ATP III) definition (18). The patients were eligible to enter the study if they were aged 25-60 and overweight ( $25 \leq \text{BMI} \leq 40 \text{ kg/m}^2$ ). Individuals with weight changes  $\geq 5\%$  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 the formula represented for parallel clinical trials, considering type 1 error ( $\alpha$ ) of 0.05 and type 2 errors ( $\beta$ ) of 0.2. The TG serum levels were 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 a 2-week 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  $520 \times g$  at  $4^\circ\text{C}$  to separate plasma from RBCs, and was stored at  $-70^\circ\text{C}$  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 ( $\text{LDL-C} = \text{total cholesterol} - \text{TG} / 2.18 - \text{HDL-C}$ ). 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:  $\text{fasting glucose (mmol/L)} * \text{fasting insulin } (\mu\text{U/L}) / 22.5$ . 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 circumference (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  $\pm$  standard deviation (SD) for continuous variables and P values  $<0.05$  were considered statistically significant.

## Results

Of 105 subjects 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 terms 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 groups 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) ( $-4.1 \pm 3.65$  vs  $-1.7 \pm 1.49$ ;  $P=0.003$ ), WC (cm) ( $-4 \pm 4.09$  vs  $-1 \pm 3.44$ ;  $P=0.026$ ), SBP (mm Hg) ( $-13 \pm 4.00$  vs  $-1 \pm 14.42$ ;  $P=0.029$ ) and FPG (mg/dl) ( $-5 \pm 6.82$  vs  $0 \pm 6.85$ ;  $P=0.009$ ) after ADF intervention in comparison with CR. Whilst, we failed to find any significant changes in BMI ( $\text{kg}/\text{m}^2$ ) ( $-1.6 \pm 2.07$  vs  $-0.8 \pm 0.90$ ;  $P=0.060$ ), TG (mg/dl) ( $-52 \pm 90.56$  vs  $-40 \pm 78.02$ ;  $P=0.614$ ), TC (mg/dl) ( $-11 \pm 24.59$  vs  $-8 \pm 31.09$ ;  $P=0.759$ ), LDL-C (mg/dl) ( $-5 \pm 20.26$  vs  $0 \pm 21.40$ ;  $P=0.289$ ), HDL-C (mg/dl) ( $-1 \pm 10.48$  vs  $0 \pm 9.35$ ;  $P=0.909$ ), DBP (mm Hg) ( $-8 \pm 7.72$  vs  $-5 \pm 12.18$ ;  $P=0.262$ ), fasting insulin ( $\mu\text{U}/\text{ml}$ ) ( $-2.41 \pm 3.21$  vs  $-1.56 \pm 5.41$ ;  $P=0.496$ ) and HOMA-IR ( $-0.72 \pm 0.92$  vs  $-0.39 \pm 1.80$ ;  $P=0.425$ ) 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 ( $5.6 \pm 1\text{kg}$ ) 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 between 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 decline 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 the 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.

**Acknowledgements:**

The authors would like to thank all the study participants. They are also grateful to the all staff for their support and cooperation.

**Conflict of interest:**

None.

**Funding:**

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

#### References:

1. Grundy SM. Metabolic syndrome update. *Trends in cardiovascular medicine*. 2016;26(4):364-73.
2. Després J-P, Lemieux I. Abdominal obesity and metabolic syndrome. *Nature*. 2006;444(7121):881.
3. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. *Circulation*. 2005;112(17):2735-52.
4. Scuteri A, Laurent S, Cucca F, Cockcroft J, Cunha PG, Mañas LR, et al. Metabolic syndrome across Europe: different clusters of risk factors. *European journal of preventive cardiology*. 2015;22(4):486-91.
5. Kassi E, Pervanidou P, Kaltsas G, Chrousos G. Metabolic syndrome: definitions and controversies. *BMC medicine*. 2011;9(1):48.
6. Saklayen MG. The global epidemic of the metabolic syndrome. *Current hypertension reports*. 2018;20(2):12.
7. Pérez-Martínez P, Mikhailidis DP, Athyros VG, Bullo M, Couture P, Covas MI, et al. Lifestyle recommendations for the prevention and management of metabolic syndrome: an international panel recommendation. *Nutrition reviews*. 2017;75(5):307-26.
8. Yamaoka K, Tango T. Effects of lifestyle modification on metabolic syndrome: a systematic review and meta-analysis. *BMC medicine*. 2012;10(1):138.
9. Kastorini C-M, Milionis HJ, Esposito K, Giugliano D, Goudevenos JA, Panagiotakos DB. The effect of Mediterranean diet on metabolic syndrome and its components: a meta-analysis of 50 studies and 534,906 individuals. *Journal of the American College of Cardiology*. 2011;57(11):1299-313.
10. Shenoy SF, Poston WS, Reeves RS, Kazaks AG, Holt RR, Keen CL, et al. Weight loss in individuals with metabolic syndrome given DASH diet counseling when provided a low sodium vegetable juice: a randomized controlled trial. *Nutrition journal*. 2010;9(1):8.
11. Tančić-Gajić M, Vujović S, Vukčević M, Ivović M, Drezgić M, Marina L, et al. Effects of alternate fasting or very low calorie diet and low calorie diet on metabolic syndrome in severely obese patients. *Hippokratia*. 2012;16(4):335.
12. Eshghinia S, Mohammadzadeh F. The effects of modified alternate-day fasting diet on weight loss and CAD risk factors in overweight and obese women. *Journal of Diabetes & Metabolic Disorders*. 2013;12(1):4.
13. Lefevre M, Redman LM, Heilbronn LK, Smith JV, Martin CK, Rood JC, et al. Caloric restriction alone and with exercise improves CVD risk in healthy non-obese individuals. *Atherosclerosis*. 2009;203(1):206-13.
14. Barnosky AR, Hoddy KK, Unterman TG, Varady KA. Intermittent fasting vs daily calorie restriction for type 2 diabetes prevention: a review of human findings. *Translational Research*. 2014;164(4):302-11.
15. Varady K. Intermittent versus daily calorie restriction: which diet regimen is more effective for

weight loss? *Obesity reviews*. 2011;12(7).

16. Varady KA, Bhutani S, Klempel MC, Kroeger CM, Trepanowski JF, Haus JM, et al. Alternate day fasting for weight loss in normal weight and overweight subjects: a randomized controlled trial. *Nutrition journal*. 2013;12(1):146.
17. Anton S, Leeuwenburgh C. Fasting or caloric restriction for healthy aging. *Exp Gerontol*. 2013;48(10):1003-5.
18. Rezaianzadeh A, Namayandeh SM, Sadr SM. National Cholesterol Education Program Adult Treatment Panel III Versus International Diabetic Federation Definition of Metabolic Syndrome, Which One is Associated with Diabetes Mellitus and Coronary Artery Disease? *International journal of preventive medicine*. 2012;3(8):552-8.
19. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMC medicine*. 2010;8(1):18.
20. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, et al. Compendium of physical activities: an update of activity codes and MET intensities. *Medicine and science in sports and exercise*. 2000;32(9; SUPP/1):S498-S504.
21. Mifflin MD, St Jeor ST, Hill LA, Scott BJ, Daugherty SA, Koh YO. A new predictive equation for resting energy expenditure in healthy individuals. *The American journal of clinical nutrition*. 1990;51(2):241-7.
22. Klempel M, Kroeger C, Norkeviciute E, Goslawski M, Phillips S, Varady K. Benefit of a low-fat over high-fat diet on vascular health during alternate day fasting. *Nutrition & diabetes*. 2013;3(5):e71.
23. Alhamdan B, Garcia-Alvarez A, Alzahrnai A, Karanxha J, Stretchberry D, Contrera K, et al. Alternate-day versus daily energy restriction diets: which is more effective for weight loss? A systematic review and meta-analysis. *Obesity science & practice*. 2016;2(3):293-302.
24. Kacimi S, Ref'at A, Fararjeh MA, Bustanji YK, Mohammad MK, Salem ML. Intermittent fasting during Ramadan attenuates proinflammatory cytokines and immune cells in healthy subjects. *Nutrition research*. 2012;32(12):947-55.
25. El Ati J, Beji C, Danguir J. Increased fat oxidation during Ramadan fasting in healthy women: an adaptative mechanism for body-weight maintenance. *The American journal of clinical nutrition*. 1995;62(2):302-7.
26. Al Hourani HM, Atoum MF, Akel S, Hijjawi N, Awawdeh S. Effects of Ramadan fasting on some haematological and biochemical parameters. *Jordan J Biol Sci*. 2009;2(3):103-8.
27. Eshghinia S, Gadgevich Gapparov M. Effect of Short-Term Modified Alternate-Day Fasting on the Lipid Metabolism in Obese Women. *Iranian Journal of Diabetes and Obesity*. 2011;3(1):1-5.
28. Bhutani S, Klempel MC, Kroeger CM, Trepanowski JF, Varady KA. Alternate day fasting and endurance exercise combine to reduce body weight and favorably alter plasma lipids in obese humans. *Obesity*. 2013;21(7):1370-9.
29. Harvie MN, Pegington M, Mattson MP, Frystyk J, Dillon B, Evans G, et al. The effects of intermittent or continuous energy restriction on weight loss and metabolic disease risk markers: a randomised trial in young overweight women. *International journal of obesity (2005)*. 2011;35(5):714.
30. Johnson JB, Summer W, Cutler RG, Martin B, Hyun D-H, Dixit VD, et al. Alternate day calorie restriction improves clinical findings and reduces markers of oxidative stress and inflammation in overweight adults with moderate asthma. *Free Radical Biology and Medicine*. 2007;42(5):665-74.
31. Klempel MC, Kroeger CM, Bhutani S, Trepanowski JF, Varady KA. Intermittent fasting combined

with calorie restriction is effective for weight loss and cardio-protection in obese women. *Nutrition journal*. 2012;11(1):98.

32. Varady KA, Bhutani S, Church EC, Klempel MC. Short-term modified alternate-day fasting: a novel dietary strategy for weight loss and cardioprotection in obese adults. *The American journal of clinical nutrition*. 2009;90(5):1138-43.

33. Wilhelmi de Toledo F, Grundler F, Bergouignan A, Drinda S, Michalsen A. Safety, health improvement and well-being during a 4 to 21-day fasting period in an observational study including 1422 subjects. *PloS one*. 2019;14(1):e0209353.

34. Trepanowski JF, Kroeger CM, Barnosky A, Klempel MC, Bhutani S, Hoddy KK, et al. Effect of alternate-day fasting on weight loss, weight maintenance, and cardioprotection among metabolically healthy obese adults: a randomized clinical trial. *JAMA internal medicine*. 2017;177(7):930-8.

35. Kroeger CM. *Alternate Day Fasting Versus Calorie Restriction for Weight Maintenance* (Doctoral dissertation) 2015.

36. Varady KA, Bhutani S, Klempel MC, Kroeger CM. Comparison of effects of diet versus exercise weight loss regimens on LDL and HDL particle size in obese adults. *Lipids in health and disease*. 2011;10(1):119.

37. Varady KA, Hellerstein MK. Alternate-day fasting and chronic disease prevention: a review of human and animal trials. *The American journal of clinical nutrition*. 2007;86(1):7-13.

38. Redon J, Cifkova R, Laurent S, Nilsson P, Narkiewicz K, Erdine S, et al. The metabolic syndrome in hypertension: European society of hypertension position statement. *Journal of hypertension*. 2008;26(10):1891-900.

39. Dewanti L, Watanabe C, Ohtsuka R. Unexpected changes in blood pressure and hematological parameters among fasting and nonfasting workers during Ramadan in Indonesia. *European Journal of Clinical Nutrition*. 2006;60(7):877.

40. Temizhan A, Dönderici Ö, Ouz D, Demirbas B. Is there any effect of Ramadan fasting on acute coronary heart disease events? *International journal of cardiology*. 1999;70(2):149-53.

41. Tinsley GM, Horne BD. Intermittent fasting and cardiovascular disease: current evidence and unresolved questions. *Future cardiology*. 2018;14(1):47-54.

42. Templeman I, Gonzalez JT, Thompson D, Betts JA. The role of intermittent fasting and meal timing in weight management and metabolic health. *Proceedings of the Nutrition Society*. 2019:1-12.