Effect of modified alternate day fasting diet on the severity of premenstrual syndrome and health-related quality of life in women with overweight or obesity: a trial study protocol

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ABSTRACT

Introduction Premenstrual syndrome (PMS) includes a range of physical, behavioural and psychological symptoms and decreases women’s health-related quality of life (HRQoL). It has been proposed that increased body mass index (BMI) is associated with menstrual problems and decreased HRQoL. The body fat amount plays a role in menstrual cycles by altering the oestrogen/progesterone ratio. Alternate day fasting as an unusual diet results in the improvement of anthropometric indices and reduction of body weight. This study aims to investigate the effect of a daily calorie restriction diet and a modified alternate day fasting diet on PMS and HRQoL.

Methods and analysis This 8-week open-label parallel randomised controlled trial examines the impact of a modified alternate-day fasting diet and daily caloric restriction on the severity of PMS and HRQoL in obese or overweight women. Using simple random sampling, women between the ages of 18 years and 50 years and 25 ≤ BMI < 40 who meet the inclusion and exclusion criteria will be chosen from the Kashan University of Medical Sciences Centre. Patients will be randomised, based on BMI and age through stratified randomisation. Then by the random numbers table, they are allocated to fasting (intervention) or daily calorie restriction (control) groups. Outcomes are chosen for the trial: the difference in the severity of PMS, HRQoL, BMI, body fat mass, fat-free mass, waist-to-hip ratio, waist circumference, hip circumference, per cent body fat, skeletal muscle mass and visceral fat area from baseline to 8 weeks.

Ethics and dissemination The Kashan University of Medical Sciences Ethics Committee has approved the trial (IR.KAUMS.MEDNT.REC.1401.003) (17 April 2022). Results will be published in peer-reviewed academic journals and the participants will be informed via phone calls.

Trial registration number IRCT20220522054958N1.

INTRODUCTION

Premenstrual syndrome (PMS) is a prevalent disorder among women of reproductive age and reduces their health-related quality of life (HRQoL). The onset of this disorder is in the luteal phase of the menstrual cycle. The worldwide prevalence of PMS is 47.8% and among Iranian women is 33–48%. The emotional, behavioural and physical symptoms of PMS might change from woman to woman and may have several reasons. Due to the role of various factors in the pathology of PMS, different therapeutic approaches are proposed for the control of symptoms, including the use of particular supplements, medications, anti-depressants, psychological approaches, dietary modifications, relaxation methods and exercise. But, researchers are investigating safer and more efficient therapies. Therefore, the use of safe approaches such as nutritional interventions for controlling this disorder can be of value. Some studies indicate that family history, age, oral contraceptive pills, stress, smoking, dietary habits, body mass index (BMI) and exercise can play a role in menstrual problems. Some data propose a positive association between menstrual problems and high BMI. In addition, Hong et al indicated a U-shaped association between menstrual problems and BMI. It indicates that both underweight and overweight/obese women have a higher risk of menstrual problems. Some studies suggest that menstrual problems are caused by increased prostaglandin

STRENGTHS AND LIMITATIONS OF THIS STUDY

- A wide range of health outcomes will be evaluated, including multiple anthropometric indices, the severity of premenstrual syndrome and measures of health-related quality of life.
- To guarantee between-group homogeneity, individuals will be randomly assigned using stratified randomisation based on body mass index and age.
- This study is not designed to evaluate the long-term consequences.
production. The body fat amount plays a role in menstrual cycles and regular ovulation and can result in menstrual problems. It can be hypothesised that irregular menstruation and disturbed ovulation can alter the oestrogen/progesterone ratio, leading to increased production of prostaglandin and menstrual problems. Also, in reviews investigating the relationship of obesity to HRQoL in various populations, obesity is associated with reduced HRQoL.

The first-line therapy for weight loss in obese patients is calorie restriction. However, because of the daily calorie restriction of conventional weight-loss diets, it is difficult to adhere to these diets. In recent years, an intermittent fasting diet has been proposed as an unusual method of losing body weight. It improves metabolic status beyond usual calorie restriction. Among the different intermittent fasting strategies that have been studied, the alternate-day fasting diet is known to be an effective method to lose weight. Alternate day fasting comprises alternating periods of fasting and feeding, on an every-other-day basis. Findings of studies indicate that alternate-day fasting reduces body weight by 3%–7% within 2–3 months. However, what has not yet been determined is whether calorie restriction or alternate day fasting will further improve anthropometric data and fat distribution. A systematic review indicated that interventions such as alternate day fasting reduce waist circumference greater than common weight-loss diets but reduce weight like daily calorie reduction diets. Several studies indicate that alternate-day fasting diet may preserve muscle mass and reduces visceral fat area compared with calorie restriction. Trepanowski et al. indicated that both alternate-day fasting and calorie restriction preserved the muscle mass, and did not change the visceral fat area. Hutchison et al. highlighted that alternate day fasting reduced weight and fat mass more than daily calorie restriction for 8 weeks. The results of other studies demonstrate that attempting weight loss increases the risk of menstrual problems. Another study indicated an increased prevalence of menstrual problems when normal BMI women entered into the class of BMI equal to or greater than 25. Also, Anton et al. showed that intermittent fasting produced significant weight loss and small but meaningful improvements in HRQoL. Etemadifar et al. indicated that Ramadan fasting improved HRQoL in patients with multiple sclerosis (MS). A fasting diet correlates with increased HRQoL independent of weight loss. A fasting-mimicking diet is feasible and safe and can potentially increase HRQOL. But Ramadan fasting could not change HRQoL in comparison with control. Therefore, we aim to study the effect of a daily calorie restriction diet and modified alternate day fasting diet on PMS and HRQoL to attain more definite findings in this field.

METHODS AND ANALYSIS

Study design

This is an open-label parallel randomised controlled trial to study the effect of a daily calorie restriction diet and alternate day fasting diet on the PMS severity and HRQoL in women with overweight or obesity for 8 weeks. Women (age: 18–50 years, BMI<40, and according to inclusion and exclusion criteria) will be recruited from the centres of Kashan University of Medical Sciences through the sampling of simple random. Then, patients are randomly allocated into groups of fasting (intervention) and daily calorie restriction (control) (table 1). The Ethics Committee of Kashan University of Medical Sciences approved the protocol of trial (IR.KAUMS.MEDNT.REC.1401.003). Also, the trial was registered at the Iranian Registry of Clinical Trials (IRCT2022052205498N1). Patients will give written consent following a verbal description of the study.

Patient and public involvement

The patients and the public are not involved in the design, conception or conduct of the trial.

Eligibility criteria

Inclusion criteria: (1) women aged 18–50, (2) their BMI is greater than or equal to 25 and less than 40, (3) regular menstrual cycles (21–35 days) and menstrual bleeding for 3–8 days and (4) having PMS.

Exclusion criteria: (1) pregnancy, (2) breast feeding, (3) a history of any chronic diseases such as heart disease, high blood pressure, diabetes, gastrointestinal disorders such as gastritis, gastric and duodenal ulcers, (4) the habit of smoking, (5) alcohol abuse, (6) weight loss more than 1–2 kg in the past month, (7) taking a dietary supplement for weight loss, (8) follow a specific diet, (9) taking any medications (such as hormonal contraception) for at least 2 months, (10) suffering from diseases that affect PMS symptoms psychological such as psychological disorders, cancer, cardiovascular diseases (CVD), hepatic, renal, infectious, neurological, endocrine and gynaecological diseases; having surgery in the past 6 months, (11) taking contraceptives and antidepressants, (12) B6 supplementation in the last 3 months, (13) suffering from severe stress during the study and (14) failure to complete the questionnaire 3 consecutive days and 5 non-consecutive days.

Sample size calculation

In the study of Fathizadeh et al., a significant difference in terms of muscle mass between the PMS and healthy groups (p<0.05) was reported. The sample size was calculated using the parameter of a previous clinical trial that investigated the effect of alternate day fasting on body composition of obese subjects. We used the fat-free mass (FFM) data for this study and the mean and the SD value of FFM (kg) were 63.4±3.4 kg in the intervention group. Therefore, we aim to study the effect of a daily calorie restriction diet on muscle mass of obese women. To detect a minimal clinically relevant difference of 3.5 kg with the condition of 80% power and the alpha error of 5%, 23 women are required for each group. Based on clinical study experience, we presume a drop-out rate of 20%, recruiting a minimum of 60 women for two groups of study.
Recruitment of participants
Participants are enrolled between August 2022 and December 2022. Subjects are recruited from the centres of Kashan University of Medical Sciences and are screened based on inclusion and exclusion criteria. Eligible participants are invited to take part in the trial. A trained nutritionist and a medical doctor assess patients according to inclusion and exclusion criteria and include patients in the study. The trained nutritionist explains the study methodology and takes informed written consent and during the entire study period contacts subjects by phone at home or work. Also, participants will be able to contact us in case of problems.

Randomisation
Fifty-six participants are recruited from the centres of Kashan University of Medical Sciences through the sampling of simple random based on the inclusion and exclusion criteria. Participants who are eligible are stratified by BMI (40>BMI≥30; 30>BMI≥25) and age (50>age≥30; 30>age≥18) to make sure homogeneity of between-groups. Patients per stratum are allocated to ‘modified alternate day fasting’ (intervention) and ‘daily calorie restriction’ (control) groups after primary assessments. An independent researcher generates the allocation sequence by random numbers table31 and a trained nutritionist enrols participants.

Study hypothesis
► Modified alternate day fasting diet reduces the severity of PMS of the patients in the fasting group.
► Modified alternate day fasting diet increases the HRQoL of the patients in the fasting group.

Study outcomes
Primary outcomes
The effect of a modified alternate day fasting diet and daily calorie restriction diet on the severity of PMS, HRQoL, BMI, body fat mass, FFM, waist-to-hip ratio and waist circumference in obese and/or overweight adult women with PMS will be assessed.

Secondary outcomes
The effect of a modified alternate day fasting diet and daily calorie restriction diet on hip circumference, percent body fat, skeletal muscle mass and the visceral fat area in obese and/or overweight adult women with PMS will be assessed.

Intervention
Figure 1 shows the flow chart of the participants. Sixty women (30 per group) with obesity or overweight and diagnosed with PMS (according to Premenstrual Symptoms Screening Tool (PSST)) are randomly assigned to the ‘alternate day fasting’ or ‘control’ group. All individuals follow their diet which will prescribe based on their total energy needs and group. The energy requirements for participants will calculate by using the Mifflin equation.32 Dietary counselling is performed by a professional dietician.

Alternate day fasting
Alternate day fasting comprises alternating periods of fasting and feasting, on an every-other-day basis. The feast and fast days begin at midnight each day. It comprises 75% caloric restriction on fasting days (only 25% of the recommended calorie intake). This intake is only authorised as lunch between 12:00 and 14:00. Subjects are
allowed to drink water and consume less than 400 mg of caffeine daily. On feasting days, the individuals consume the total of their daily energy requirements. All participants will prepare their meals at home and continue their diet for 8 weeks. Daily dietary fat, protein and carbohydrates, respectively, account for 30%, 15% and 55% of energy requirement.

**The daily calorie restriction**

In the daily calorie restriction (control) group, subjects consume 63% of the calculated energy requirement each day. Participants continue their diet for 8 weeks and prepare their meals at home. Daily dietary fat, protein and carbohydrates, respectively, account for 30%, 15% and 55% of energy requirement. Subjects in control and intervention groups are required to keep their physical activity routine throughout the study.

**Adherence and participant retention**

To control the adherence of the participants to their diets, food record is taken from the participants every 2 weeks, 1 day off and 2 days during the week\(^{33}\) and will be compared with the recommended diet. To accurately complete the questionnaires, all individuals are given information on how to complete the questionnaire, units of measurement and a selection of appropriate days to complete the forms. The information obtained from the food record questionnaires is converted to grams using the home scale guide and then analysed using N4 software (First Databank; Hearst Corporation) adopted for the Iranian foods and the amount of energy and macronutrients received is calculated. Patients have adequate adherence when a total caloric intake is 80%–110% of the prescribed.\(^{34}\) Researchers will make phone calls to patients every 2 weeks to encourage them to continue what they are doing.

**Criteria to stop or change assigned treatments based on certain standards**

- Individuals with bad adherence are those whose calorie consumption is below 80% or greater than 110% of their daily calorie intake.
Participants who experience intense emotional tension within the trial.

Pregnancy within the trial.

Data management and protection
The study only involves a limited number of participants, so the data monitoring committee is not necessary. Moreover, data will be retained in local and cloud storage as well as SPSS programme (version 22). There is no personal information about the participants in the information. Results will be presented as an overall total. Although efforts will be made to keep participants’ information confidential, sometimes patient information may be reviewed by university representatives for purposes such as safety or quality control.

Harms
Researchers will monitor and assess any adverse events that may be connected to the study intervention. The patients will receive ongoing observation. The Kashan University of Medical Sciences and the Kashan University of Medical Sciences Ethics Committee will be notified if any negative occurrences arise throughout the course of the study. The attending physician oversees any such event, and the trial fund pays for the expense.

Assessment of variables
Premenstrual symptoms screening tool
To diagnose PMS and assess the severity of premenstrual symptoms, we use the PSST questionnaire. It consists of 19 questions which have two parts. A part includes 14 psychological, behavioural and physical symptoms and another part measures the effect of these symptoms on people’s lives and includes 5 questions. These symptoms are assessed in the 5 days before menstruation. The intensity of symptoms is graded from 1 to 4 (1: none, 4: severe). To recognise a PMS patient, the following schedule is used: (1) a score greater than or equal to 3 in one of the 4 questions about whether the woman felt ‘tense’, ‘irritable’, ‘depressed’ or ‘tearful’, (2) a score greater than or equal to 3 in one of the 5 variables of interference with “relationship with colleagues, family members, work performance, in social life or household tasks” and (3) a score greater than or equal to 3 in at least 4 of the first 14 questions. Women who do not have the requirements are excluded from the trial.

Calendar of Premenstrual Experiences
After the selection of participants with PMS, they are expected to record their daily experience of symptoms using the COPE for 3 months. The COPE is a reliable and valid tool consisting of 22 premenstrual symptoms to measure the 10 most commonly reported somatic and the 12 most commonly reported behavioural symptoms daily within the menstrual cycle. The severity of items is assessed daily using a 4-point Likert scale (0=not at all; 1=a little; 2=somewhat; 3=a great deal). The scores are summed at the end of each month and then the severity of PMS is calculated as a percentage. If the number is less than 30%, the severity of PMS is mild. If this number is 30% or more and less than 50%, the severity of the syndrome is moderate and if this number is between 50% and 60%, the severity of the syndrome is severe and if this score is more than 60%. The severity of the syndrome is considered to be very severe. This form will be completed by the participants for 3 months, 1 month before the start of the intervention, and will be completed for 2 months during the intervention.

12-item short-form health survey
The 36-item Short Form Health Survey (SF-36) is a generic HRQoL questionnaire that is widely used worldwide. SF-12 is a shorter alternative form of the SF-36 that involves 12 questions and 8 scales: bodily pain, physical functioning, role limitations because of physical problems, vitality, general health, role limitations because of emotional problems, social functioning and perceived mental health. Response categories for items are ranging from 1 to 6 point scales. Then raw scores are transformed to provide 8 scale scores grading from 0 to 100. And a higher score means a better HRQoL.

Physical activity scale
To evaluate physical activity in this trial, the physical activity questionnaire based on the metabolic equivalents (METs) is used. This questionnaire has 9 levels from sleep and rest (METs: 0.9) to severe activity (>6 METs).

Anthropometric indices
BMI: weight was measured using the scale (Seca Scale, Germany) with an accuracy of 0.1 kg. Individuals’ weight is measured without shoes and with a light dress. Height is measured using a stadiometer with an accuracy of 0.5 cm, standing and without shoes. BMI is evaluated as weight in kilograms divided by height squared in metres.

The waist circumference is measured by a trained nutritionist during normal expiration at the midpoint between the highest point of the iliac crest and the lowest rib, with a non-stretchable measuring tape, so that we can be sure that the tape is horizontal to the floor. Waist circumference is measured twice and if the deviation is too large (>1 cm), it is measured a third time.

Other anthropometric indices such as per cent body fat, FFM, skeletal muscle mass, body fat mass, visceral fat area and waist-to-hip ratio are measured by the bioelectrical impedance analysis method (InBody 770; InBody Co.). All anthropometric indices are measured before and after the intervention.

Statistical assessment
In this study, the Kolmogorov-Smirnov test is used to investigate the compliance of the data with the normal distribution. A $\chi^2$ test is applied to make comparisons of qualitative variables between the two groups (alternate day fasting and control) and an independent t-test is applied to detect changes in quantitative factors between groups. Quantitative data are displayed as mean and SD. A paired t-test (in parametric conditions) and Wilcoxon
test (in non-parametric conditions) are applied to make comparisons of the mean of quantitative data within the group at the beginning and end of the intervention (8 weeks later). The t-test (in parametric conditions) and the Mann-Whitney test (in non-parametric conditions) are applied to make comparisons of the mean between the two groups. Analysis of covariance (ANCOVA) is applied to detect the differences in variable changes between the two groups before and after the study. P-values <0.05 are considered statistically significant and the data are analysed using SPSS software (version 13, IBM). Two subgroup analyses will be conducted, with possible interaction effects and strong biological rationale. ANCOVA and multiple regression models will be used to investigate whether the treatment effect interacts with specific covariates and whether specific variables are confounding for the treatment effect.

DISCUSSION
In this study, for the first time, the impact of a modified alternate-day fasting diet on the severity of premenstrual syndrome is examined. Previous studies have shown the association of obesity with premenstrual problems and reduced HRQoL. The body fat amount plays a role in menstrual cycles and regular ovulation and can result in menstrual problems. The first-line therapy for weight loss in obese patients is calorie restriction. However, because of the daily calorie restriction of conventional weight-loss diets, it is difficult to adhere to these diets. Recently, the fasting diet has been introduced as a popular diet. The results of a study indicated that 8 weeks of alternate day fasting resulted in higher weight and fat tissue losses versus daily calorie restriction. Although the association between obesity and premenstrual problems has been shown in previous studies, some investigations have reported an increase in menstrual problems when participants attempt to lose weight. Therefore, this trial is conducted to evaluate the effect of a modified alternate day fasting diet and daily calorie restriction diet on PMS and HRQoL to achieve more definite results in this field. These findings will enhance our understanding of fasting diets, which can improve clinical dietary recommendations for women with PMS. Also, this trial will provide important findings regarding the effectiveness of alternate day fasting in people with overweight or obesity.

Ethics and dissemination
The investigation has been registered in the Iranian Registry of Clinical Trials (IRCT202020522054958N1). Before participants give written, informed consent, they will receive the necessary information about the trial. Participants will be informed that they can withdraw from the research at any time. All collected information will be coded and kept in secure locations. There is no psychological or physical harm associated with the trial. The findings of this study will be published in national and international conferences and scientific journals. The trial is approved by the Ethics Committee of Kashan University of Medical Sciences (IR.KAUMS.MEDNT.REC.1401.003) (17 April 2022).

Consent
A trained nutritionist in the research assesses the participants, explains the trial methodology and takes informed written consent. Necessary measures will be taken for any patient who is injured within this research, and if necessary, compensation will be paid and events associated with the research will be administered free of cost. Data from participants contain no information on participants’ identities. The participant consent form’s patient data will be kept in separate folders for future reference.

Access to data
A trained nutritionist will keep the information in external storage and cloud storage. A statistician will analyse the data. Throughout the trial, data will not be accessible to researchers. There is no arrangement to restrict access for researchers.

Contributors SJ conceived the trial and is the dietician of the trial. SHH and AY significantly contributed to development of the study protocol. SHH contributed to acquiring ethical approval for the trial and wrote the final manuscript. SJ, SHH and AY contributed to collection, analysis and interpretation of data. AY contributed to the statistical analysis. All authors reviewed and contributed to the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

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REFERENCES
6 Freeman EW. Therapeutic management of premenstrual syndrome. Expert Opin Pharmacother 2010;11:2879–89.


